CORRELATION OF HEPATIC VENOUS PRESSURE GRADIENT WITH TRANSIENT ELASTOGRAPHY IN PATIENTS WITH CIRRHOTIC PORTAL HYPERTENSION

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Dedicated

to

my Family

&

Teachers

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Dr. Kanav Grover

ABBREVIATIONS

ALD	Alcoholic liver disease
APRI	Aspartate aminotransferase/platelet ratio index
ARFI	Acoustic radiation force impulse
CPS	Child-Pugh score
CSPH	Clinically significant portal hypertension
FHVP	Free hepatic venous pressure
HBV	Hepatitis-B virus
HCV	Hepatitis-C virus
HVPG	Hepatic venous pressure gradient
IVC	Inferior vena cava
kPa	Kilopascals
LS	Liver stiffness
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NPV	Negative predictive value
PPV	Positive predictive value
RA	Right atrium
ROI	Region of interest
ROC	Receiver operating curve
SPH	Severe portal hypertension
SS	Spleen stiffness
SWE	Shear wave elastography
TE	Transient Elastography
UGIE	Upper gastro-intestinal endoscopy
VITRO	Von Willebrand Factor Antigen/Thrombocyte Ratio
VSPH	Very severe portal hypertension
WHVP	Wedged hepatic venous pressure

KEY TO MASTERCHART

S. No.	Serial number
F	Female
M	Male
NASH	Non-alcoholic steatohepatitis
UGI	Upper gastrointestinal
HE	Hepatic encephalopathy
CPS	Child-Pugh Score
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
NR	Non-reactive
HVPG	Hepatic venous pressure gradient
TE	Transient elastography
UGIE	Upper GI endoscopy
ANA	Anti-Nuclear antibody
ASM	Anti-Smith antibody

ABSTRACT

Introduction: The result of any insult to the liver is hepatic fibrosis, cirrhosis, and portal hypertension. The progression of portal hypertension can predict various complications of cirrhosis. Measuring the hepatic venous pressure gradient (HVPG) is the ideal method to quantify portal hypertension, however, it is an invasive procedure. Transient elastography (TE) is a non-invasive modality that measures the degree of liver fibrosis, suggesting that it could be a good modality to evaluate portal hypertension.

Aims: 1. To identify a possible correlation between HVPG and transient elastography in cirrhotic patients. 2. To investigate whether TE can serve as a non-invasive diagnostic test to identify patients who have clinically significant portal hypertension.

Materials and Methods: The study was conducted at Dayanand Medical College and Hospital, Ludhiana; on consecutive patients who underwent HVPG and TE during a specific period. Correlation between HVPG and TE was analysed using ROC curves to determine the utility of TE in predicting various stages of portal hypertension.

Results: In our study, 65.7% of the patients were males. The commonest etiology for cirrhosis was NASH-related liver disease (45.7%). 30 patients (85%) had clinically significant portal hypertension (CSPH) i.e. HVPG ≥ 10 mmHg while 28 patients (80%) had severe portal hypertension i.e. HVPG > 12 mmHg. A fair correlation was noted between TE and HVPG (Spearman's rho correlation coefficient 0.847, $p < 0.001$). A TE cut-off of 16.5 kPa predicted CSPH with a sensitivity and specificity of 96.6% and 80.0% respectively, with a positive predictive value of 96% and a negative predictive value of 80%.

Conclusion: In cirrhotic patients with portal hypertension, HVPG has a fair correlation with TE values. TE may serve as a reliable non-invasive modality to predict the development of clinically significant portal hypertension.

Keywords: Hepatic venous pressure gradient, transient elastography, clinically significant portal hypertension

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INTRODUCTION

BACKGROUND

The end-result of injury to the liver due to any cause is hepatic parenchymal fibrosis, cirrhosis and eventually the development of portal hypertension.[1] Portal hypertension is defined as a pathological increase in portal venous pressure. This increase in pressure causes the pressure gradient between the portal vein and the inferior vena cava (portal pressure gradient) to increase above the normal range (1–5 mmHg). When this portal pressure gradient increases to ≥10 mmHg, complications of portal hypertension can arise. These complications include formation of portosystemic collaterals and varices, upper gastrointestinal bleeding resulting from ruptured gastroesophageal varices, ascites, renal dysfunction and hepatic encephalopathy. The measurement of portal hypertension is important, as a progressive increase in portal pressure is believed to predict various complications of cirrhosis.[2]

Although mortality related to cirrhosis has been decreasing globally especially in the West, it has been steadily increasing in India since 1980. Alcohol consumption (the commonest cause of cirrhosis in India) and the prevalence of diabetes (a major risk factor for non-alcoholic fatty liver disease - NAFLD); have been steadily increasing in South Asia.[3] The International Diabetes Federation has revised its estimates of the number of people with diabetes in South-East Asia from 50 million in 2009 to 78.3 million in 2015, with a projection of 140 million by 2040.[4,5]

With 188,575 liver cirrhosis deaths in 2010, India ranks number one in the world in deaths related to cirrhosis, accounting for almost one-fifth (18%) of global deaths.[6] With such a huge population of cirrhotic patients in India whose etiology differs significantly from the West, an easy and non-invasive modality for estimation of portal hypertension is needed.

Hepatic venous pressure gradient (HVPG) is the ideal method for the measurement of portal hypertension and the prediction of complications that arise from it.[7,8] The normal hepatic venous pressure gradient is between 1-5 mmHg, while HVPG >5mmHg is defined as portal hypertension. Porto-systemic collaterals develop at HVPG greater than 10 mmHg, and variceal bleeding could occur from varices when the pressure increases to greater than 12 mmHg. An HVPG greater than 10 mmHg is used as the cut-off for “clinically significant portal hypertension” (CSPH).[9]

HEPATIC VENOUS PRESSURE GRADIENT (HVPG)

HVPG represents the gradient between pressures in the portal vein (wedged HPV) and the intra-abdominal portion of inferior vena cava (free HVP). When blood flow in a hepatic vein is stopped by a wedged catheter (WHVP), the proximal static column of blood transmits the pressure from the preceding communicating hepatic sinusoids to the catheter. In the normal liver, WHVP reflects hepatic sinusoidal pressure and not the portal pressure itself.[10] Thus, HVPG is the difference between the wedged hepatic venous pressure (WHVP) and the free hepatic venous pressure (FHVP) of a major hepatic vein.

HVPG = WEDGED HVP – FREE HVP

PROCEDURE

HVPG is measured by introducing Swan-Ganz catheter into a major hepatic vein and thus, is an invasive procedure. Fasting for 8 hours is needed pre-procedure. Catheterization of the hepatic vein is carried out under sedation in conjunction with non-invasive vital sign monitoring. Under local anaesthesia, the right jugular vein (or the femoral or antecubital vein) is catheterized, a venous introducer is placed, and a balloon-tipped catheter is advanced under fluoroscopic guidance into the inferior vena cava and a hepatic vein to measure WHVP, FHVP, pressure in the inferior vena cava (IVC) and right atrium (RA).

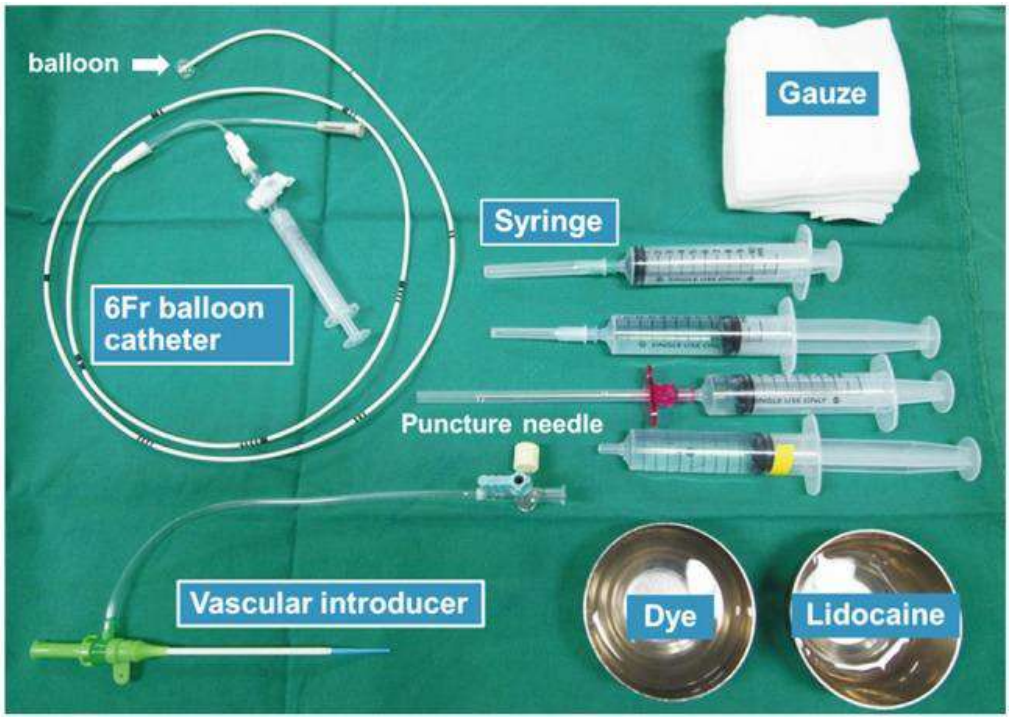

Figure 1: Standard procedure equipment for HVPG measurement.[11]

Standard procedure equipment for HVPG measurement:

- Fluoroscopy machine
- Local anesthetic
- Puncture needle
- Vascular introducer
- Swan-Ganz balloon catheter
- Contrast dye
- Pressure recorder
- Pressure transducer

Further equipment such as an electrocardiography monitor and O2 saturation monitor is needed for non-invasive vital sign monitoring.[11]

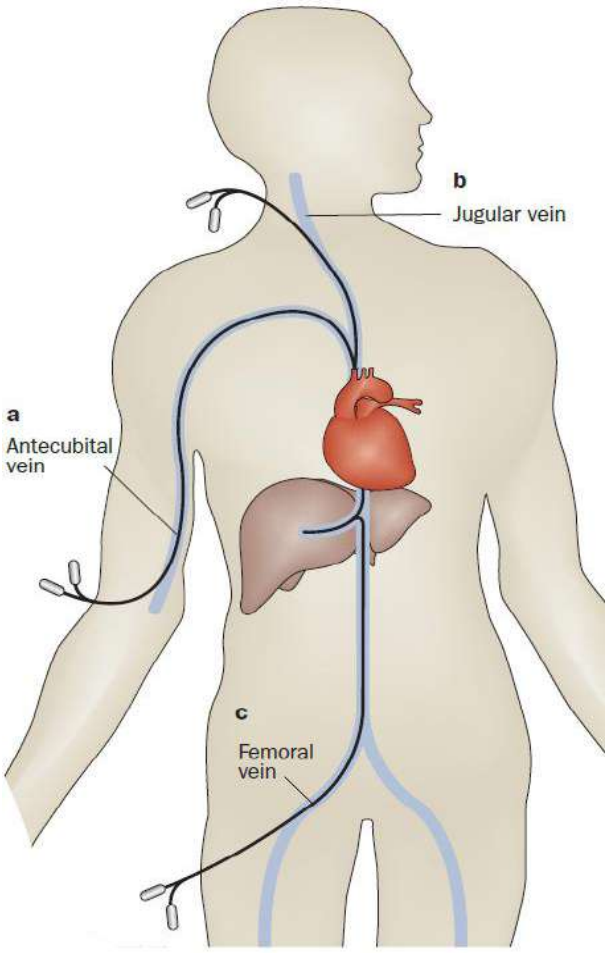

Figure 2: Venous access sites for hepatic vein catheterization. a: antecubital vein, b: jugular vein, c: femoral vein can be used for hepatic vein catheterization. The trans-jugular approach is the one most frequently used, as it enables a transvenous liver biopsy to be obtained as part of the procedure.[11]

FREE HEPATIC VENOUS PRESSURE (FHVP)

FHVP is measured by maintaining the tip of the catheter 'free' in the hepatic vein, at 2–4 cm from its opening into the inferior vena cava. The FHVP should be similar in value to the inferior vena cava pressure. A difference of >2 mmHg signifies that the catheter is probably inadequately placed.

WEDGED HEPATIC VENOUS PRESSURE (WHVP)

WHVP is measured by occluding the hepatic vein, either by 'wedging' the catheter into a small branch of a hepatic vein or by inflating a balloon at the tip of the catheter. Adequate occlusion of the hepatic vein is confirmed by slowly injecting 2 ml of contrast dye into the vein without observing reflux of the dye or its washout through communications with other hepatic veins.

NORMAL VERSUS CIRRHOTIC LIVER

In the normal liver, after occlusion of blood flow in a hepatic vein with a balloon catheter, the pressure of the static column of blood, (wedged hepatic venous pressure) equilibrates through the interconnected sinusoids. WHVP, therefore, is a measurement of the hepatic sinusoidal pressure which is slightly lower than the portal pressure (by ~1 mmHg).

In the cirrhotic liver, the pressure of the static column of blood created by balloon inflation cannot be decompressed at the sinusoidal level owing to the narrowing and disruption of the normal inter-sinusoidal architecture due to fibrosis. Consequently, WHVP equilibrates with and is equivalent to portal pressure in the cirrhotic liver.[12]

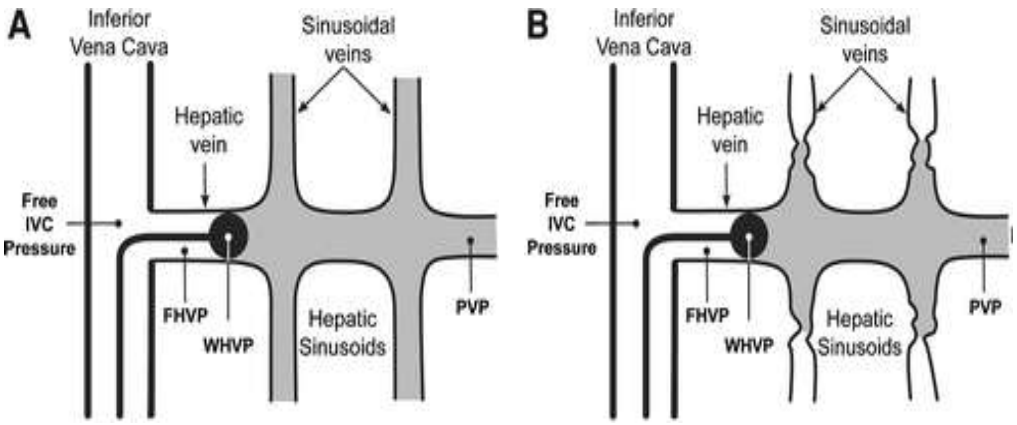

Figure 3: Measuring the portal pressure in the normal and cirrhotic liver. In liver cirrhosis, the static column created by balloon inflation cannot be decompressed at the sinusoidal level due to disruption of the normal inter sinusoidal communications; therefore, WHVP gives an accurate estimation of portal pressure in cirrhosis.[12]

The normal HVPG value is between 1 to 5 mmHg. Pressure higher than this defines the presence of portal hypertension. HVPG ≥10 mmHg (clinically significant portal hypertension) is predictive of the development of complications of cirrhosis. HVPG >12 mmHg (severe portal hypertension) is the threshold pressure for variceal rupture.[13,14] Thus, the measurement of HVPG predicts long-term mortality in patients with compensated [15] as well as decompensated cirrhosis.[16] As evident, HVPG is an invasive procedure that requires training and expertise.[17]

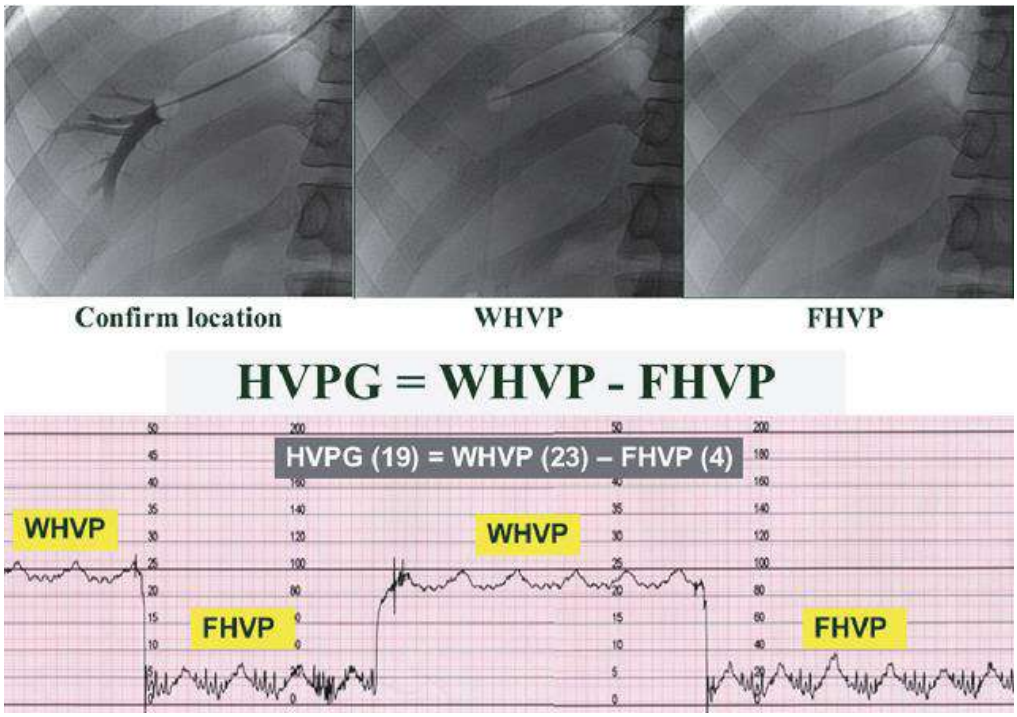

Figure 4: Method for HVPG measurement. HVPG (Hepatic venous pressure gradient) = (Wedged – Free) hepatic venous pressure.[17]

Many non-invasive tests have been reported to predict the presence of clinically significant portal hypertension (CSPH) in patients with cirrhosis with variable accuracy. The ideal non-invasive diagnostic test for portal hypertension should be simple, inexpensive, widely accessible, and reliable in measurement and interpretation.

TRANSIENT ELASTOGRAPHY

Transient elastography (TE) is a rapid, non-invasive, ultrasound-based technology that allows the measurement of liver stiffness.[18,19] It has demonstrated excellent sensitivity and specificity for diagnosing liver fibrosis and cirrhosis.[20,21]

In addition, its cost-effectiveness, better patient acceptability and ease of availability have witnessed a substantial increase in its usage for the assessment of liver fibrosis.[22]

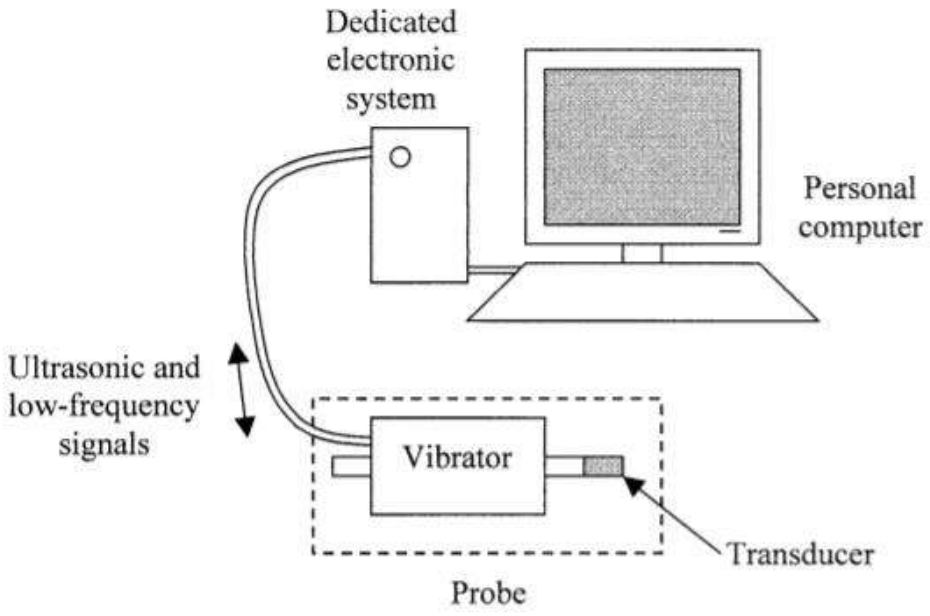

Figure 5: Components of a Fibroscan® setup: probe, dedicated electronic system and control unit [23]

TE consists of an ultrasound transducer mounted on the axis of a vibrator, which produces vibrations of a mild amplitude and low frequency (50 Hz), consequently inducing an elastic shear wave that propagates through the liver parenchyma.[23]

PRINCIPLE

The basic principle of TE is that the propagation velocity of a wave through a homogenous tissue is proportional to its elasticity, which is correlated with the amount of fibrosis in the liver.[24] Pulse-echo ultrasound follows the propagation of the shear wave and measures its velocity, which is related to liver tissue stiffness.[25] The low-frequency elastic wave is largely a shear wave, which presents a longitudinal component. Its propagation velocity is of the order of 1m/s whereas compressional ultrasonic waves are very fast (about 1500 m/s). The liver is considered a non-viscous, isotropic, soft elastic medium. Under these approximations, Young's modulus, *E* is expressed as

$$E = 3\rho V^2_s$$

where $V^2_s$is the shear wave velocity and ρ is the mass density. In soft tissues, mass density is approximately constant and close to that of water. Therefore, a mass density of 1000 kg/m^3 is used by default.

It is seen that the velocity of elastic waves is faster in fibrotic liver than in normal livers. The slope of propagation velocity of the wave pattern increases as a function of fibrosis grading. The reading is measured in Kilopascals (kPa).[26,27]

MEASUREMENT ACQUISITION

During the acquisition, patients lie supine with their right arm extended behind their head. The physician first proceeds to localize the region of interest. A minimal liver parenchymal thickness of 6 cm is sought. Regions with large vessels are avoided. The Fibroscan® probe is placed in the intercostal position in front of the chosen ultrasonic window and readings are taken as a consecutive series of 10 validated measurements, without moving the patient.

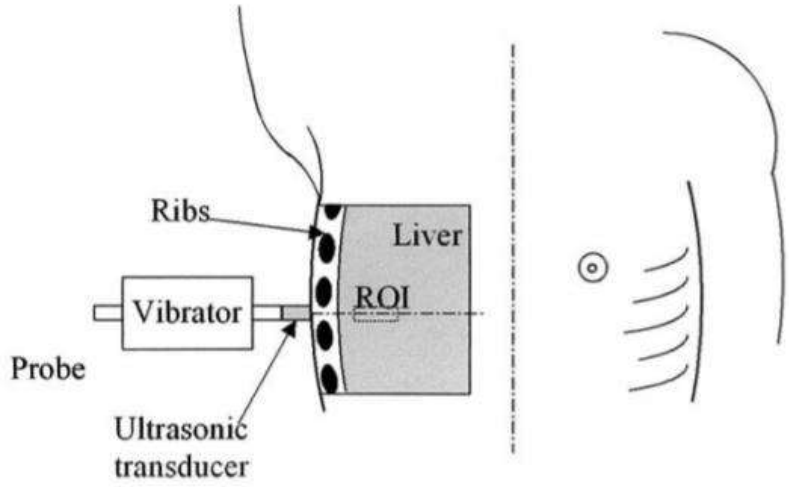

Figure 6: Probe positioning for liver stiffness measurement[26]

Elasticity is derived from the velocity of the low-frequency elastic wave in an ROI located from 2.5 to 4.5 cm below the skin surface. This ROI is chosen to avoid the subcutaneous tissue and the liver fibrous capsule in most of the patients and to ensure that the signal to noise ratio is optimum.

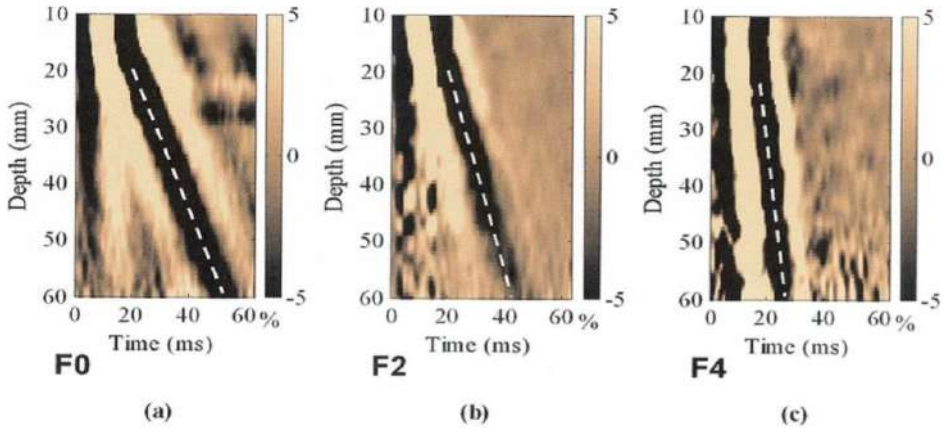

Figure 7: Elastic wave propagation in livers with different fibrosis grades. The slope of the white dotted lines represents the propagation velocity of the wave pattern that increases as a function of fibrosis grading.[27]

Although there may be some discrepancy between the degree of fibrosis encountered in viral versus non-viral cirrhosis[28, 29], there is a general consensus that the degree of fibrosis is proportional to the clinical outcomes and the eventual development of long-term

complications including esophageal varices.[30,31] This makes transient elastography a potentially promising modality to non-invasively diagnose and quantify liver fibrosis and hence indirectly, albeit theoretically predict the development of portal hypertension.

Other newer and promising non-invasive modalities are being developed for diagnosing portal hypertension, such as two-dimensional shear wave elastography (2D-SWE)[32-35]; acoustic radiation force impulse (ARFI)[36-38]; VITRO Score (Von Willebrand Factor Antigen/Thrombocyte Ratio)[39]; aspartate aminotransferase/platelet ratio index (APRI)[40]; spleen elastography[41,42]; and serum tests such asFibrosis-4[43,44], and Lok score.[45,46]

AIMS & OBJECTIVES

- To identify a possible correlation between HVPG and transient elastography in cirrhotic patients
- To investigate whether TE can serve as a non-invasive diagnostic test to identify patients who have clinically significant portal hypertension

REVIEW OF LITERATURE

The earliest study correlating transient elastography (TE) measurements with hepatic venous pressure gradient (HVPG) readings was done by Carrion et al in 2006, who prospectively evaluated the diagnostic accuracy of non-invasive measurement of liver stiffness by transient elastography in 124 hepatitis C related cirrhotic patients simultaneously undergoing HVPG measurements. They identified a significantly high correlation of transient elastography with HVPG [Correlation coefficient (*r)* = 0.840].[47]

In 2007, Vizzuti et al in their study on 61 HCV related cirrhotic patients found that the correlation was excellent for HVPG values less than 10 or 12 mmHg (r = 0.81 and r = 0.91, respectively); however, the linear regression analysis was not optimal for HVPG values ≥ 10 mmHg (r = 0.59) or ≥ 12 mmHg (r = 0.37). They hypothesized that in advanced portal hypertension, it was not only the liver fibrosis but also the extrahepatic factors, such as the increase in blood flow due to hyperdynamic circulation, that may have contributed to portal hypertension.[48]

Lemoine et al in 2008 attempted to assess the relationship between TE and HVPG measurements in patients with compensated cirrhosis related to hepatitis-C virus (HCV) and alcoholic liver disease and to define the performance and the best cut-off of liver stiffness (TE) values for the diagnosis of significant portal hypertension in these subsets. They evaluated a cohort of 92 patients out of which 44 had HCV-related cirrhosis and 48 had alcoholic liver disease (ALD) related cirrhosis. Liver stiffness measurements were positively correlated to HVPG in both groups. They found that the best TE cut-off values for the diagnosis of significant portal hypertension was 20.5 kPa in HCV patients, while it was higher at 34.9 kPa in ALD-related cirrhosis.[49]

Bureau et al in 2008 demonstrated that transient elastography accurately predicted the presence of significant portal hypertension in patients with chronic liver disease.

They measured liver stiffness by Fibroscan® in 150 consecutive patients who underwent liver biopsies and hemodynamic measurements. HVPG was found to be correlated with TE values (rho = 0.858; p< 0.001). The TE cut-off value of 21 kPa accurately predicted significant PHT in 92% of the 144 patients.[50]

Sánchez-Conde et al in 2011performed hepatic hemodynamic studies (HVPG) and TE in 38 HIV/HCV-coinfected patients. The association between HVPG and liver stiffness was assessed by linear regression. They found a statistically significant association between liver stiffness (kPa) and HVPG (r^2 = 0.46, P < 0.001).[51]

The largest of these studies has been done by Reiberger et al in 2012, who retrospectively correlated transient elastography and HVPG in 502 patients.

A significant correlation of LS and HVPG was noted (R = 0.794; p< 0.0001), being stronger in patients with viral disease (R = 0.838; p< 0.0001) than in patients with alcoholic disease (R = 0.756; p< 0.0001). The LS cut-off at 18 kPa was able to identify CSPH with a PPV and NPV of 86% and 80%, respectively.[52]

Llop et al in 2012 suggested two cut-offs of TE instead of one to predict CSPH. They showed that a cut-off of 13.6 kPa was sufficiently sensitive to exclude CSPH, and a cut-off of 21 kPa was sufficiently specific to include CSPH. They suggested that values in between these limits (which were found in 35% of their patients) were not useful and termed these patients as being in the “grey zone”. They believed that the use of a single TE cut-off limits the value of TE to predict CSPH. The use of at least two cut-offs reproduces the clinical thinking in which a diagnostic test commonly provided three outputs, i.e. the condition is either included, excluded or “further tests were needed”.[53]

Further in 2012, Abraldes et al evaluated the role of liver biopsy, transient elastography and hepatic venous pressure gradient (HVPG)

in the diagnosis and monitoring of patients with liver cirrhosis. They argued that although transient elastography had some role in the non-invasive diagnosis of cirrhosis, relevant information was lost if it was used as a dichotomous test to diagnose clinically significant portal hypertension, as a large proportion of patients had non-diagnostic values. They further added that a single non-invasive marker was not a practical substitute for endoscopic screening of varices. Rather, a combination of liver stiffness (measured by Fibroscan), spleen size (measured by ultrasound) and platelet count were accurate in predicting the presence of high-risk varices and variceal bleeding.[54]

In a cross-sectional study to look for non-invasive markers of the presence of CSPH and esophageal varices, Berzigotti et al in 2013 assessed the ability of platelet count, spleen diameter, liver stiffness (LS) in isolation as well as in combinations to identify patients with CSPH and esophageal varices in 117 patients with compensated cirrhosis. They concluded that LS was the best single non-invasive variable for identifying patients with CSPH ($r = 0.824\text{-}0.943$; $P < .0001$). The predictive value further increased when LS was used with platelet count and spleen size in combinations.[55]

Hong et al in 2013 evaluated the relationship between LS measurements and HVPG, and the predictive value of LS for clinically significant portal hypertension (HVPG ≥10 mmHg) and severe portal hypertension (HVPG ≥12 mmHg) in 59 cirrhotic patients.

A strong positive correlation between LSM and HVPG was observed in the overall population ($r^2=0.496$, $P<0.0001$). The area under the ROC curve (AUROC) for the prediction of CSPH (HVPG ≥10 mmHg) was 0.851, and the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for an LSM cut-off value of 21.95 kPa were 82.5%, 73.7%, 86.8%, and 66.7%, respectively.[56]

A meta-analysis by Shi et al in 2013 evaluated a total of 18 studies, which included 3644 patients, for the diagnostic accuracy of TE for

significant portal hypertension. Their data also indicated that TE had high accuracy for the detection of significant portal hypertension. The hierarchical summary receiver-operating characteristic (HSROC) for the diagnosis of significant portal hypertension by TE was 0.93 (95%CI: 0.90-0.95).[57]

Augustin et al in 2014 evaluated a sequential screening-diagnostic strategy based on clinical data and transient elastography (TE) to detect PH in asymptomatic patients with liver disease. Consecutive patients with chronic liver disease and no previous diagnosis of PH were screened by TE. Patients with liver stiffness (LS) ≥ 13.6 kPa were further evaluated by endoscopy and hepatic venous pressure gradient (HVPG) They found out that out of the 40 patients who underwent HVPG, a TE value cut-off of 26kPa was very useful at ruling-in CSPH.[58]

In 2015 Zykus et al further assessed the correlation between liver or spleen stiffness measurement by transient elastography (TE) and hepatic venous pressure gradient (HVPG) in patients with chronic liver disease. The study included 107 consecutive patients referred for HVPG measurement. Successful spleen TE was performed in 99 of the patients. Liver and spleen TE strongly correlated with HVPG, $r = 0.75$ and $r = 0.62$, respectively. Accuracy to detect CSPH was 88.7% for liver stiffness of 17.4 kPa. Accuracy to detect SPH was 83.1% for liver stiffness of 20.6 kPa. Liver stiffness <11.4 kPa could rule out CSPH with 55.2% specificity and >21.9 kPa could rule in CSPH with 74.4% sensitivity. Overall, liver elastography was found to be superior to spleen elastography in predicting portal hypertension.[59]

Elkrief et al in 2015 prospectively compared the technical success rate and accuracy of shear-wave elastography (SWE) and transient elastography (TE) for the detection of clinically significant portal hypertension in patients with advanced cirrhosis. Seventy-nine consecutive patients with cirrhosis who were undergoing SWE and TE at the time of HVPG measurement were studied. The technical

success rate of SWE and TE was compared with the diagnostic value of liver stiffness (LS) and spleen stiffness (SS) measurements. LS of more than 24.6 kPa had a sensitivity, specificity, and accuracy for clinically significant portal hypertension of 81%, 88%, and 82%, respectively. Thee diagnostic performance of LS was statistically better than that for spleen stiffness for the diagnosis of clinically significant PH (area under the receiver operating characteristic curve of 0.87 vs 0.64, P = .003).[60]

Procopet et al in 2015 assessed the diagnostic accuracy of six serum scores in isolation and in combination with liver stiffness measured by transient elastography, for diagnosing cirrhosis, clinically significant portal hypertension and oesophageal varices. 202 consecutive compensated patients requiring liver biopsy and hepatic venous pressure gradient measurements were included. Artificial neural networks were also created for comparison.

They demonstrated that the best non-invasive method for diagnosing cirrhosis, portal hypertension and oesophageal varices was liver stiffness (C-statistics = 0.93, 0.94, and 0.90, respectively). The use of artificial scores using different non-invasive tests did not increase the diagnostic accuracy of liver stiffness used in isolation.[61]

Kitson et al in 2015 evaluated LS as a non-invasive tool in the prediction of CSPH and portal hypertensive complications. Ninety-five consecutive patients successfully underwent measurement of hepatic venous pressure gradient (HVPG) and LS. Patients were followed up for the development of portal hypertensive complications.[62]

Furthermore in 2015, Schwabl et al evaluated the utility of a new TE reliability criterion suggest classifying measurements as very reliable (IQR/M < 0.1), reliable (IQR F<0.3 or >0.3, if TE < 7.1 kPa) and poorly reliable (IQR/M > 0.3, if TE > 7.1 kPa). They further attempted to identify potential confounders of TE performance.

Among 226 cirrhotic patients, of which 75.7% had a viral etiology, traditional TE quality criteria identified 71.6% reliable measurements, while new criteria yielded in 83.2% accurate results. Reliable TE values according to both criteria significantly correlated with fibrosis stage (r = 0.648 vs. r = 0.636) and HVPG (r = 0.836 vs. r = 0.846.).[63]

Kumar et al in their study in 2017 study included 326 patients and identified a significant positive correlation between TE and HVPG (rho 0.361, $p < 0.001$). The area under ROC curve for TE in predicting CSPH was 0.740 (95%CI: 0.662-0.818) ($p < 0.01$). A cut-off value of TE of 21.6 kPa was found to best predict CSPH with a positive predictive value (PPV) of 93%.[64]

MATERIALS & METHODS

SOURCE OF DATA

The study was conducted at Dayanand Medical College and Hospital, Ludhiana; on patients who underwent HVPG and TE during a specific period.

Each included patient underwent a detailed evaluation in terms of demographic parameters, etiology of cirrhosis and assessment of the severity of liver disease (Child-Pugh scores). A standard methodology was followed for the measurement of liver stiffness by TE and measurement of HVPG.

METHOD OF COLLECTION OF DATA

The study was retrospective on prospectively enrolled patients during this period. A total of 35 patients were included in the study.

HVPG was measured by introducing Swan-Ganz catheter into a major hepatic vein. Patients were kept fasting for 8 hours pre-procedure. Catheterization of the hepatic vein was carried out under sedation in conjunction with non-invasive vital sign monitoring. Under local anaesthesia, the right jugular vein (or the femoral or antecubital vein) was catheterized, a venous introducer was placed, and a balloon-tipped catheter was advanced under fluoroscopic guidance into the inferior vena cava and a hepatic vein to measure WHVP, FHVP, pressure in the IVC and RA.

For TE measurements, patients lied supine with their right arm extended behind their head. The Fibroscan® probe was placed in intercostal position in the chosen ultrasonic window and readings were taken as a consecutive series of 10 validated measurements, without moving the patient.

INCLUSION CRITERIA

Patients with cirrhosis and portal hypertension, greater than 18 years of age who underwent HVPG and TE were included in the study. Both these procedures were performed within an interval of two months.

EXCLUSION CRITERIA

The following patients were excluded from the study:

(1) Patients with non-cirrhotic cause of portal hypertension

(2) Patients with acute-on-chronic liver failure

(3) Patients with an invalid reading of TE or whose HVPG was not possible due to technical reasons

(4) Patients with a concomitant extra-hepatic malignancy

DURATION OF STUDY

One year. 1st May 2019 to 1st May 2020.

STATISTICAL ANALYSIS

Data was described in terms of range; mean ± standard deviation (±SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. Correlation between HVPG and TE was analysed using the Spearman's correlation test. Receiver operating characteristic (ROC) curves were prepared for determining the utility of TE in predicting various stages of portal hypertension. The best cut-off value of TE for the diagnosis of CSPH was obtained using the Youden index. All statistical calculations were done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows.

OUTCOME

- To identify a possible correlation between HVPG and transient elastography in cirrhotic patients
- To investigate whether TE can serve as a non-invasive diagnostic test to identify patients who have clinically significant portal hypertension

OBSERVATIONS AND RESULTS

The study was conducted at Dayanand Medical College and Hospital, Ludhiana; on patients who underwent HVPG and TE during a specific period. Each included patient underwent a detailed evaluation in terms of demographic parameters, etiology of cirrhosis, assessment of the severity of liver disease (Child-Pugh scores). A standard methodology was followed for the measurement of liver stiffness by TE and measurement of HVPG.

Table 1: Sex distribution

Sex	No. of cases	Percentage
F	12	34.2%
M	23	65.7%
Total	35	100%

In our study, 65.7% of the patients were males and 34.2% were females. The male to female ratio was 1.9:1

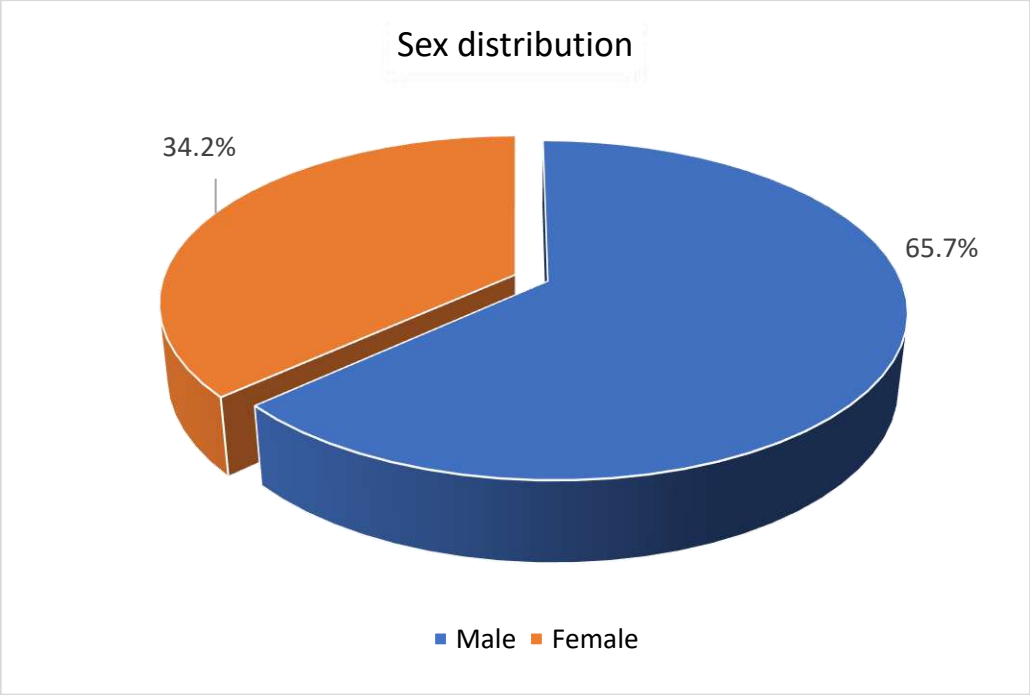

Figure 8: Sex distribution

Table 2: Age distribution

Age group (in years)	No. of patients	Percentage
11-20	4	11.4%
21-30	3	8.5%
31-40	2	5.7%
41-50	5	14.2%
51-60	13	37.1%
61-70	7	20.0%
71-80	1	2.8%
Total	35	100%

In this study, most of the patients were aged between 51 to 60 years (37.1%).

The mean age was found to be 51 years.

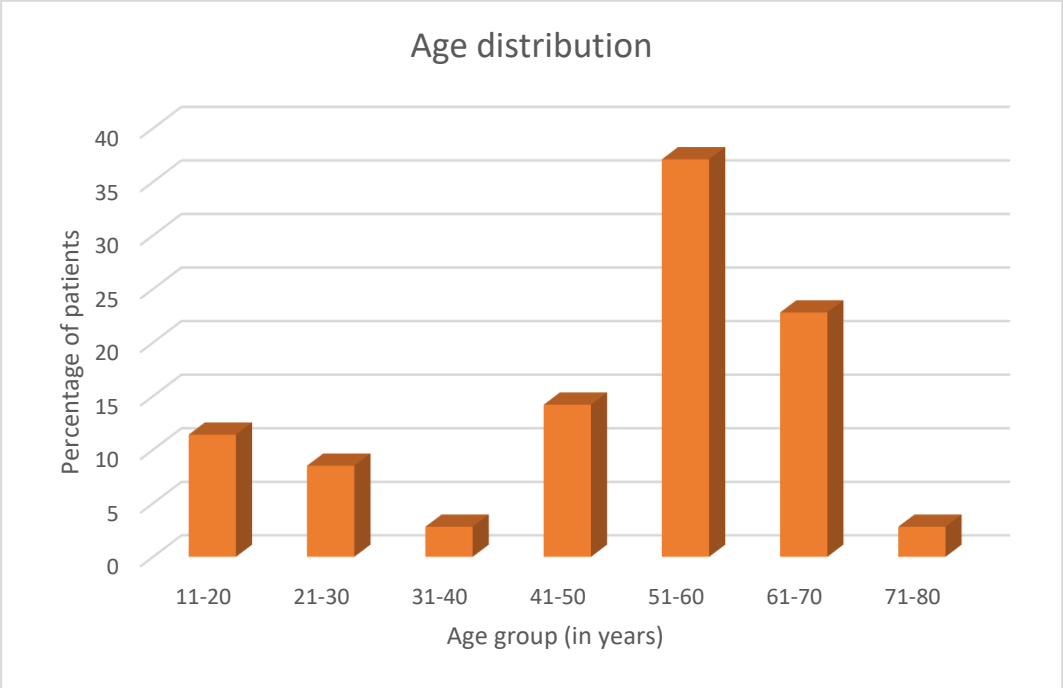

Figure 9: Age distribution

Table 3: Etiology of cirrhosis

Etiology of cirrhosis	No. of patients	Percentage
NASH related	16	45.7%
Alcoholic liver disease	8	22.8%
Infective	3	8.5%
Auto-immune	4	11.4%
Drug induced injury	4	11.4%
Total	35	100%

The most common etiology of cirrhosis was NASH-related liver disease (45.6%) followed by alcoholic liver disease (22.8%).

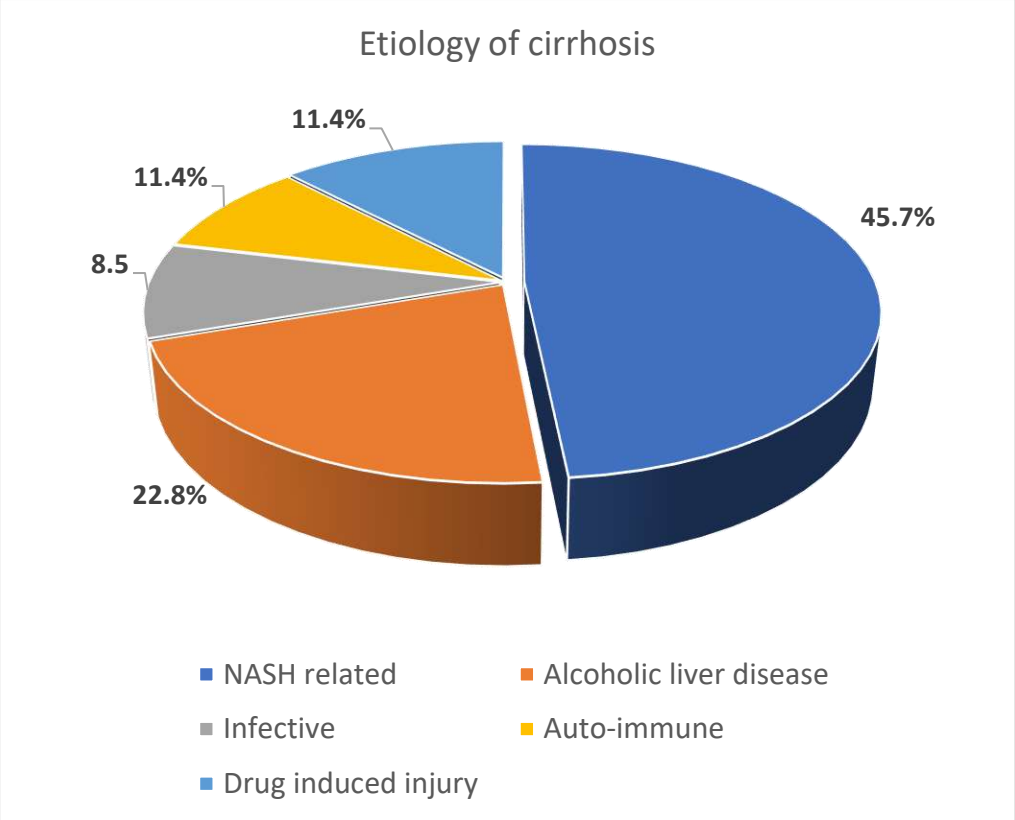

Figure 10: Etiology of cirrhosis

Table 4: Severity of cirrhosis

Child-Pugh Score	No. of cases	Percentage
A	20	57.1%
B	14	40.0%
C	1	2.8%
Total	35	100%

According to the severity of chronic liver disease, 19 patients fell into Child-Pugh group A, 13 patients were in Child-Pugh group B while 1 patient was in Child-Pugh group C.

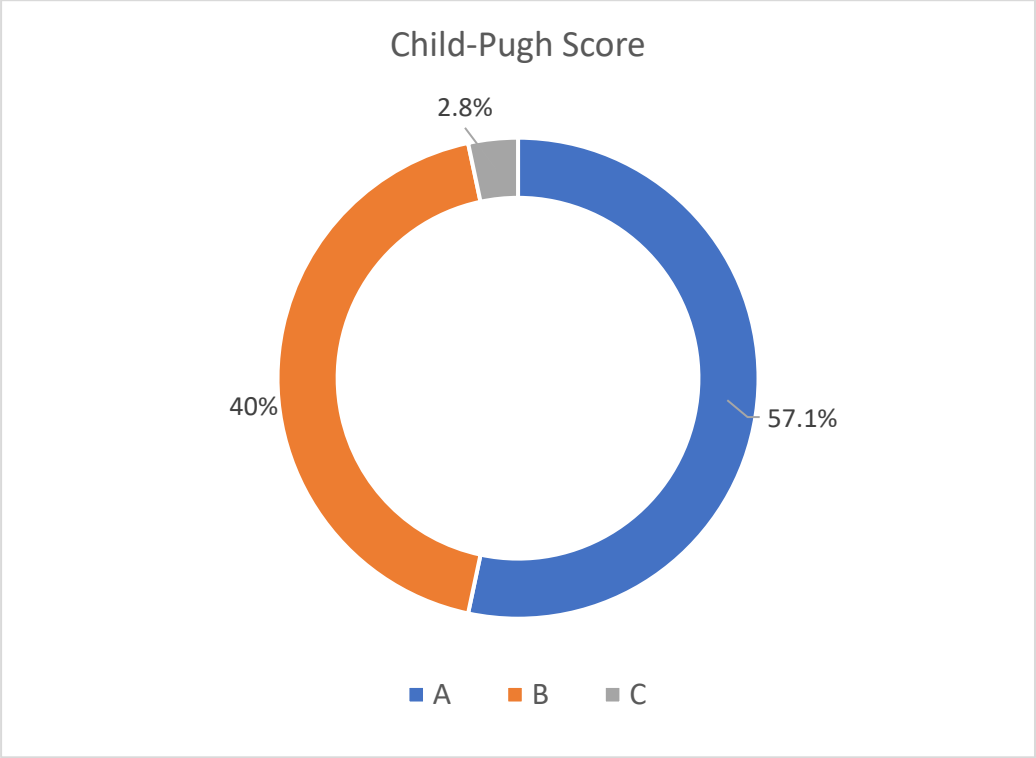

Figure 11: Severity of cirrhosis according to Child-Pugh scores

Severity of esophageal varices

Out of the 23 patients that had undergone upper GI endoscopy, six patients had no esophageal varices. Eight patients had grade 1 varices. Four patients demonstrated grade 2 varices, while five patients had grade 3 esophageal varices. 85% of patients were non-bleeders, whereas the remaining had bled from varices.

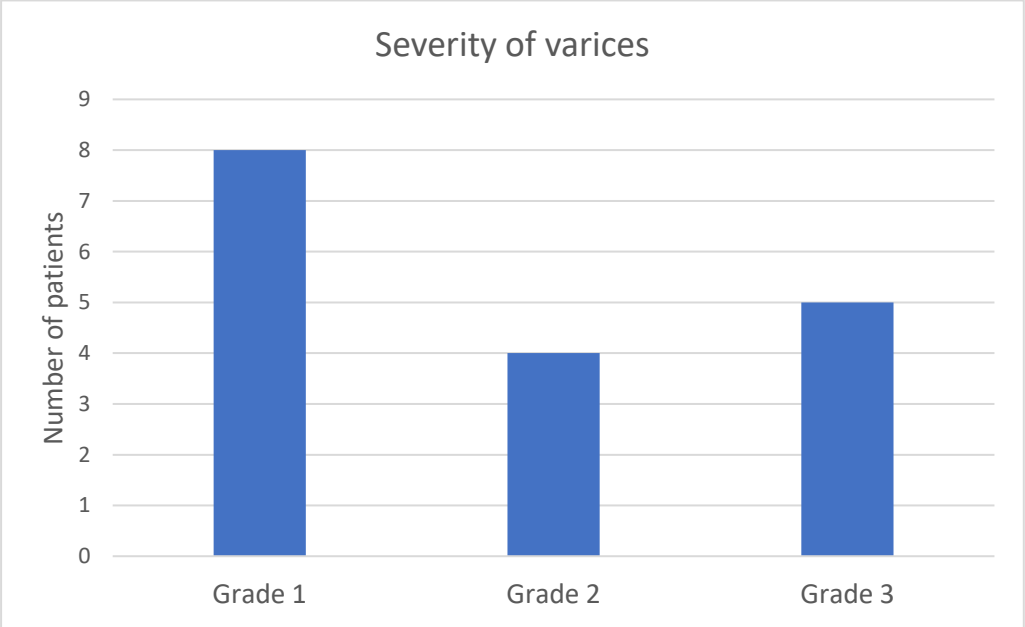

Figure 12: Severity of esophageal varices

Correlation of TE with HVPG

The median HVPG measurement was 17 mmHg with a range of 4 to 31 mmHg. The median liver stiffness (transient elastography) value was 26.7 kPa with a range of 4.2 to 66.4 kPa.

A fair correlation was noted between liver stiffness and HVPG levels (Spearman's rho correlation coefficient 0.847, $p < 0.001$).

HVPG value could be predicted by the following formula:

$HVPG = -0.0064TE^2 + 0.73TE + 0.77$

The adjusted R squared value was 0.714

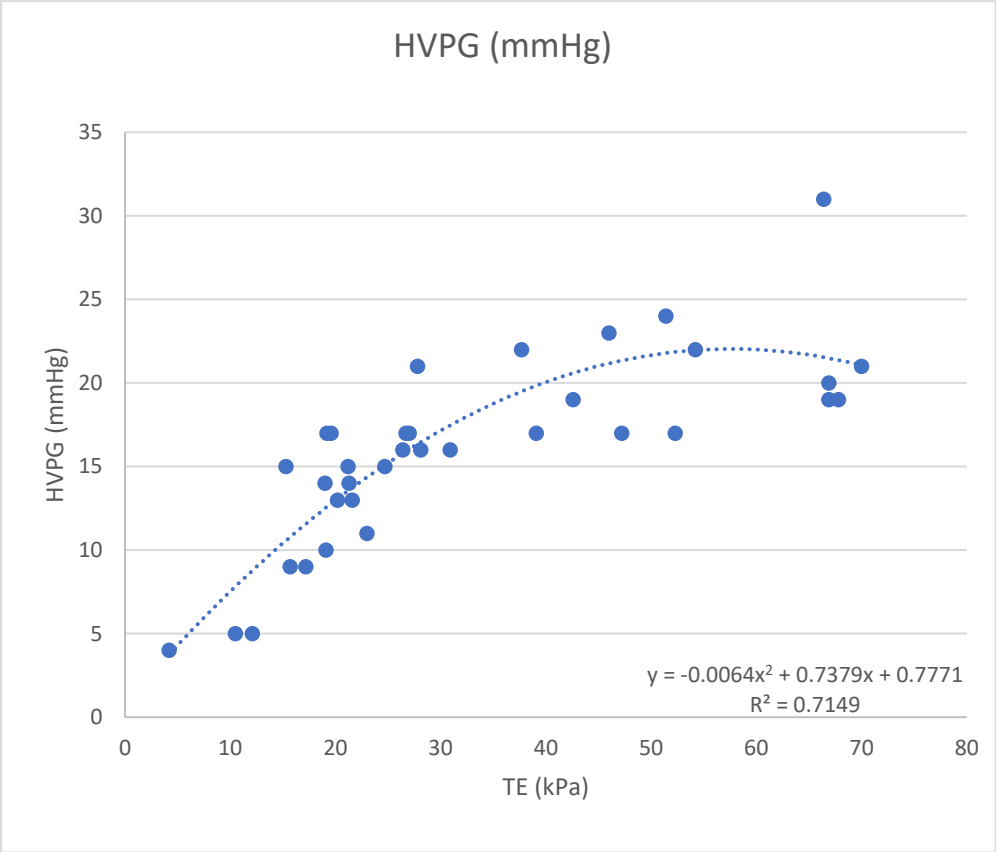

Figure 13: Scatter-plot of transient elastography and hepatic venous pressure gradient values. HVPG: Hepatic venous pressure gradient

TE values in patients with various stages of portal hypertension

Figure 14 represents the median TE values in various stages of portal hypertension measured by HVPG. There was a progressive rise in TE values with increasing stages of portal hypertension.

Patients with HVPG >5 to <10 mmHg (sub-clinical portal hypertension) had a median TE value of 13.9 (range 10.5 to 15.7) kPa.

Patients with HVPG ≥ 10 to 12 mmHg had a median TE value of 21.05 (range 19.1 to 23) kPa.

Patients with HVPG > 12 to ≤ 20 mmHg had a median TE value of 26.5 (range 11.6 to 67.8) kPa.

Patients with HVPG > 20 mmHg had a median TE value of 52.8 (range 27.8 to 66.9) kPa.

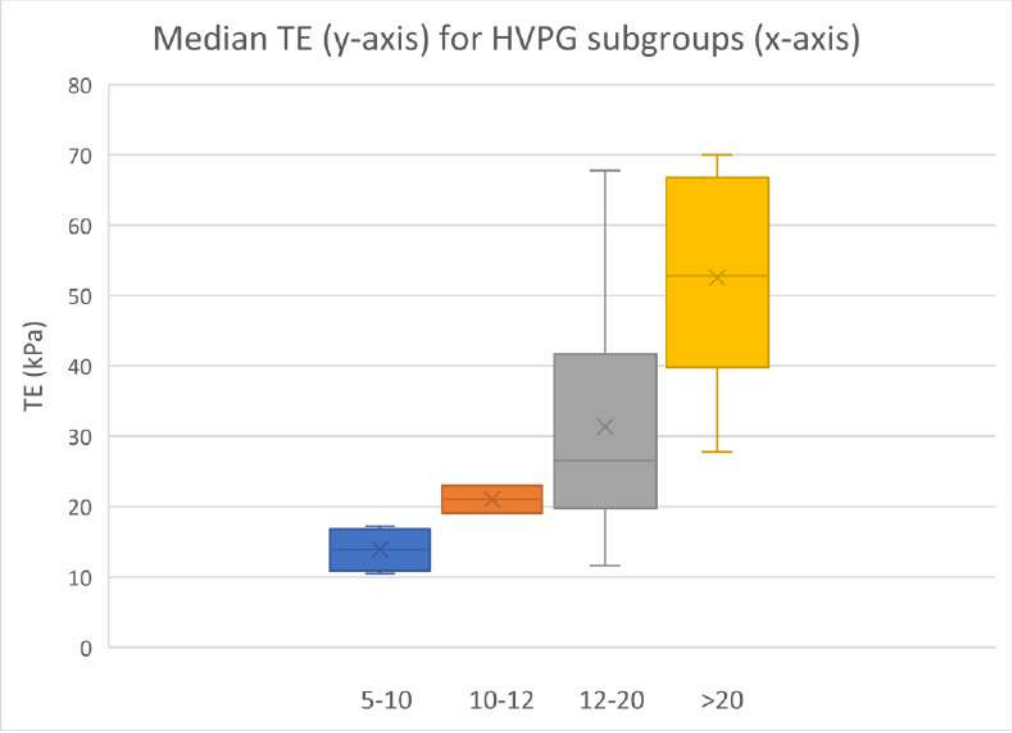

Figure 14: Median TE values in patients with various stages of portal hypertension (HVPG)

Performance of TE in predicting various stages of portal hypertension

Figures 15.1 to 15.4 represent the ROC curves of TE for predicting the various stages of portal hypertension.

ROC curve of TE at HVPG >5 mmHg

34 out of 35 (97%) patients had portal hypertension (HVPG > 5 mmHg). TE proved to be a reliable non-invasive modality in predicting portal hypertension with an area under the ROC curve of 1.0 with a *p*-value of <0.01.

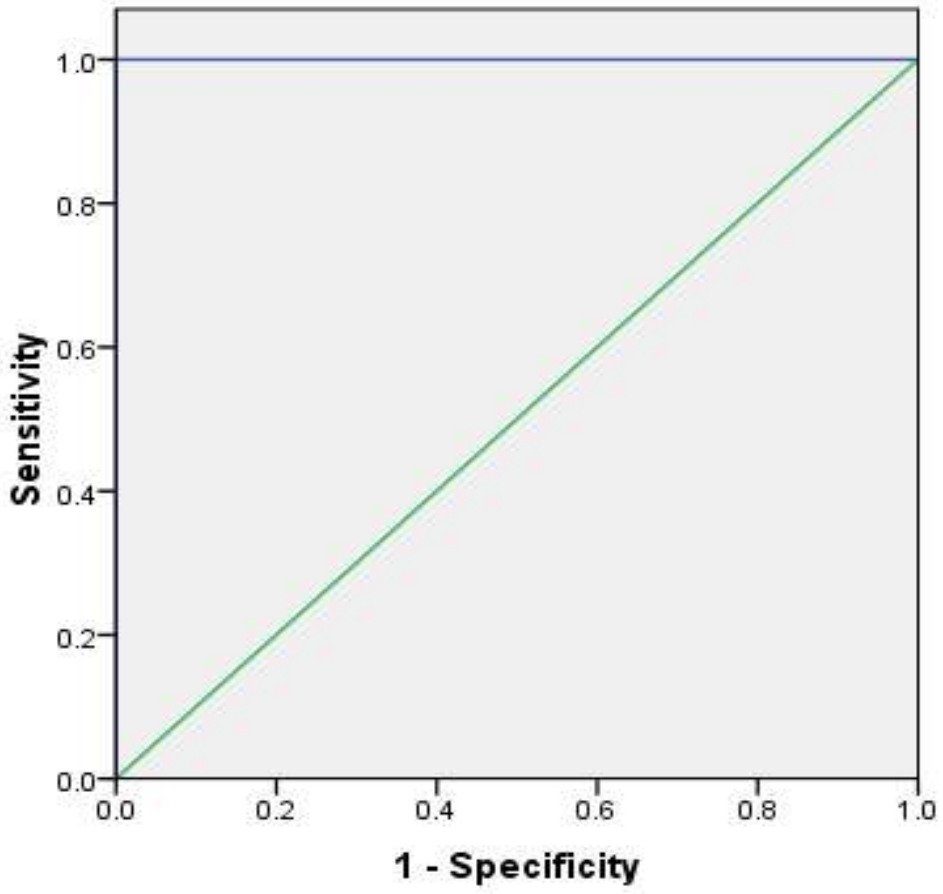

Figure 15.1: ROC curve of TE at HVPG >5 mmHg

ROC curve of TE at HVPG ≥10 mmHg

30 patients (85%) had clinically significant portal hypertension (HVPG ≥ 10 mmHg).

The area under the ROC curve for TE in predicting CSPH was 0.987 with a *p*-value of <0.01.

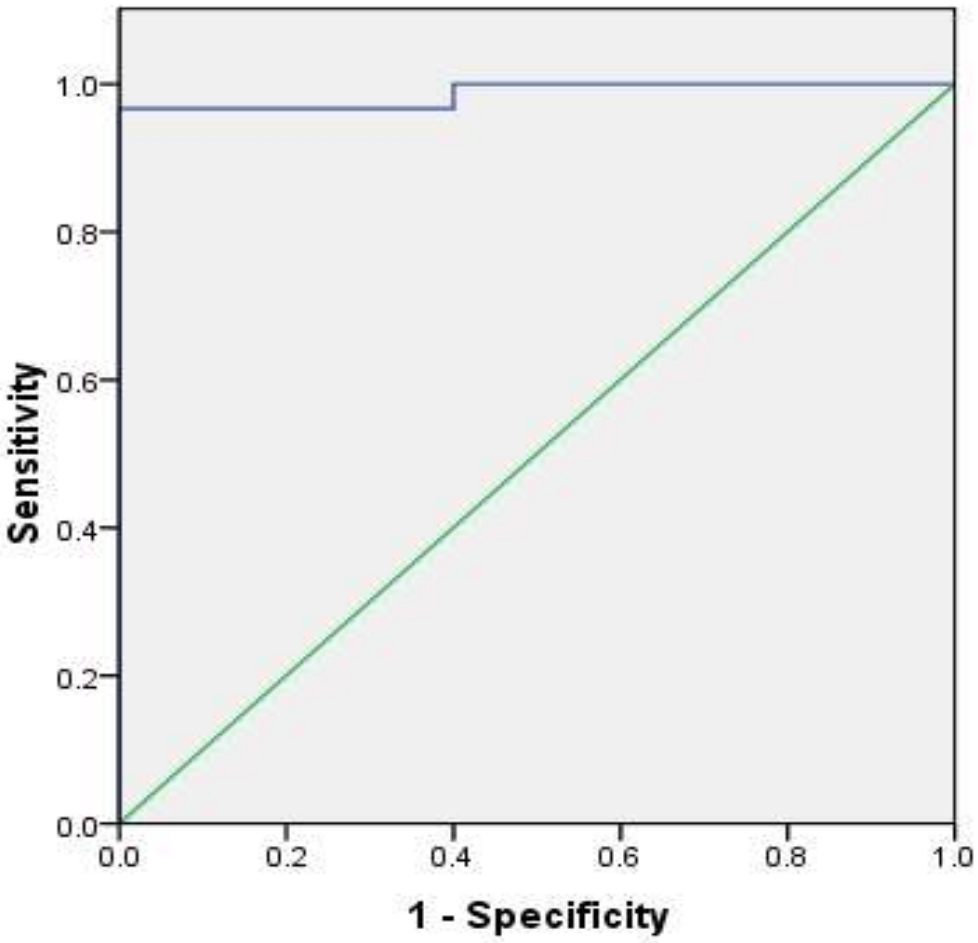

Figure 15.2: ROC curve of TE at HVPG ≥10 mmHg

ROC curve of TE at HVPG >12 mmHg

28 patients (80%) had severe portal hypertension (HVPG > 12 mmHg) which is the threshold for variceal bleeding.

The area under the ROC curve for TE in predicting HVPG > 12 mmHg was 0.939 with a *p*-value of <0.01.

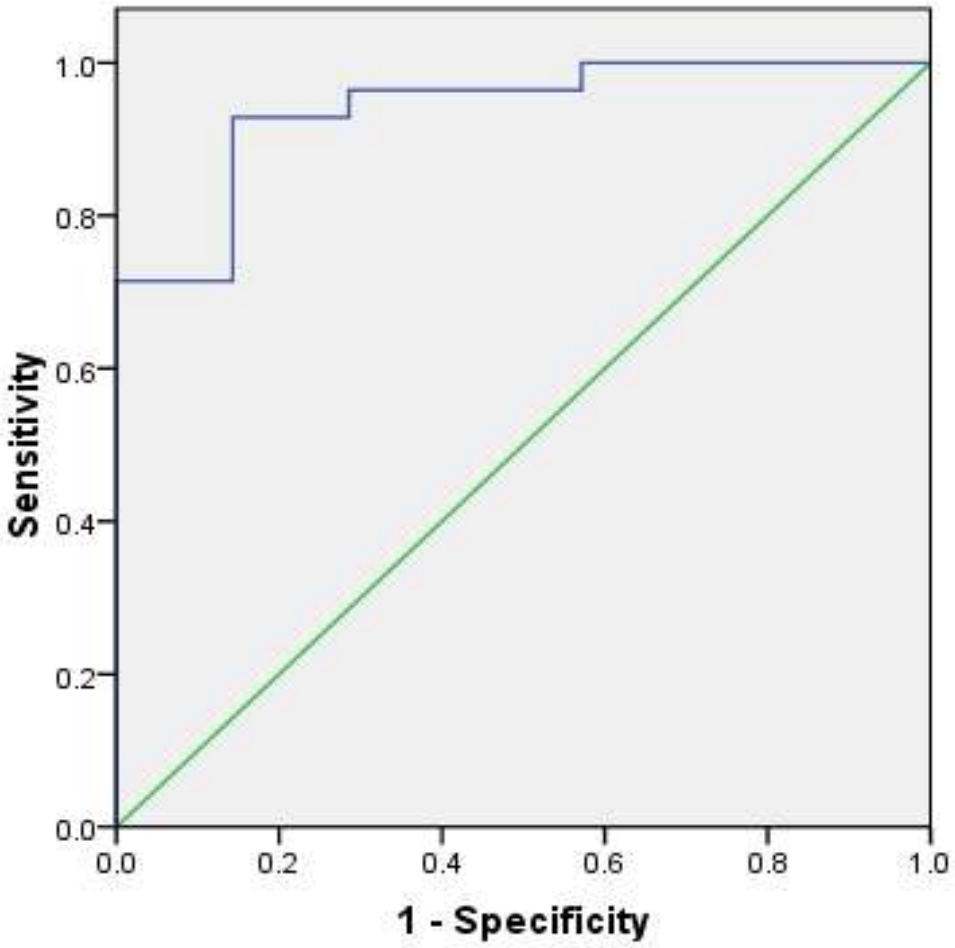

Fig 15.3: ROC curve of TE at HVPG >12 mmHg

ROC curve of TE at HVPG >20 mmHg

7 patients (20%) had very high portal hypertension (HVPG > 20 mmHg).

The area under the ROC curve for TE in predicting HVPG > 20 mmHg was 0.842 with a *p*-value of <0.01.

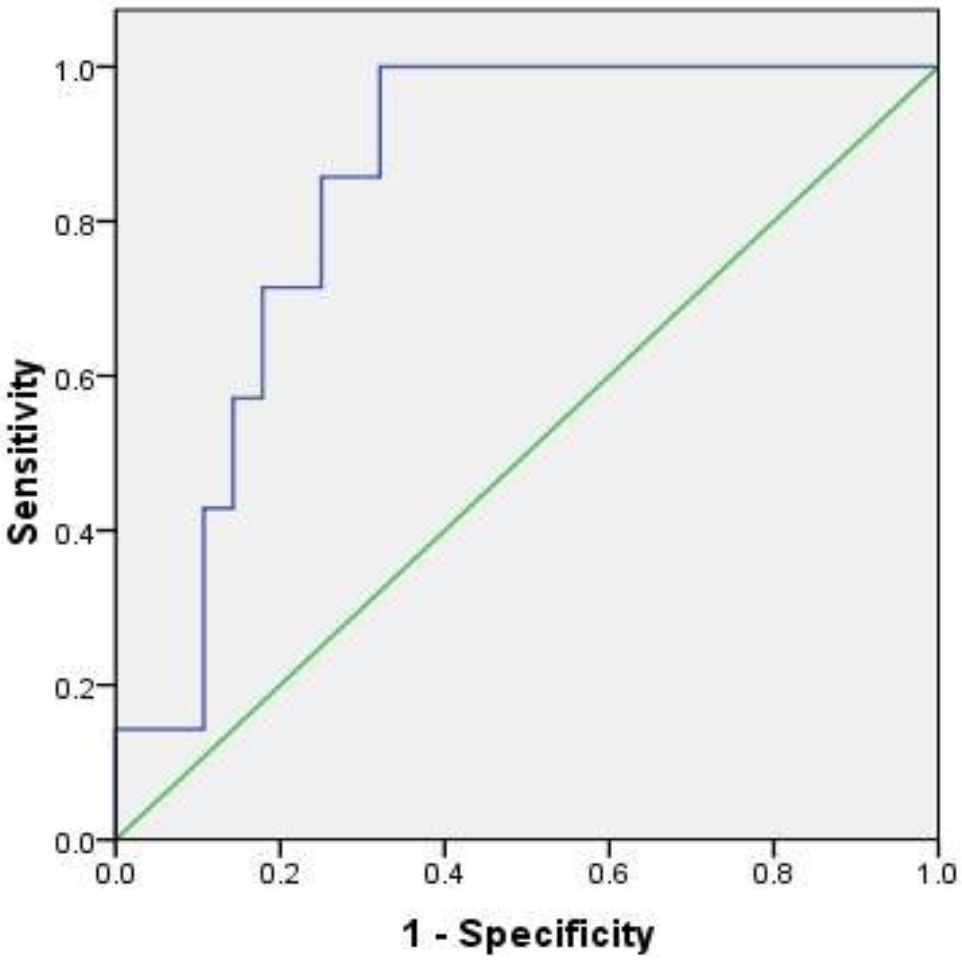

Fig 15.4: ROC curve of TE at HVPG >20 mmHg

Table 5: Cut-off TE value for predicting clinically significant portal hypertension (HVPG ≥ 10 mmHg)

		HVPG (mmHg)		Total	Chi-square value	p-value
		< 10	≥ 10			
TE (kPa)	< 16.5	4	1	5	20.572	0.0001
	> 16.5	1	29	30		
Total		5	30	35		

HVPG is ≥10 mmHg is known as clinically significant portal hypertension (CSPH). Most complications of portal hypertension occur at or above this value. The area under the ROC curve for TE to diagnose CSPH was 0.987.

A cut-off value of TE of 16.5 kPa was obtained by using Youden index to best predict CSPH. The sensitivity and specificity of this cut-off value to predict CSPH was 96.6% and 80.0% respectively with a positive predictive value (PPV) of 96% and a negative predictive value (NPV) of 80%.

Tables 5 and 6 represent the predictive values of transient elastography for the prediction of clinically significant portal hypertension (HVPG ≥10 mmHg).

Statistic	Value	95% CI
Sensitivity	96.67%	82.78% to 99.92%
Specificity	80.00%	28.36% to 99.49%
Positive Likelihood Ratio	4.83	0.84 to 27.93
Negative Likelihood Ratio	0.04	0.01 to 0.30
Disease prevalence	85.71%	69.74% to 95.19%
Positive Predictive Value	96.67%	83.38% to 99.41%
Negative Predictive Value	80.00%	35.66% to 96.65%
Accuracy	94.29%	80.84% to 99.30%

Table 6: Predictive values of TE cut-off for clinically significant portal hypertension (HVPG ≥10 mmHg)

Table 7: Cut-off TE value for predicting severe portal hypertension (HVPG > 12 mmHg)

		HVPG (mmHg)		Total	Chi-square value	p-value
		< 12	> 12			
TE (kPa)	< 21.25	6	6	12	10.272	0.001
	> 21.25	1	22	23		
Total		7	28	35		

The area under the ROC curve for TE to diagnose severe portal hypertension (HVPG >12 mmHg) was 0.939. A cut-off value of TE of 21.2 kPa was obtained by using Youden index to best predict SPH.

The sensitivity and specificity of this cut-off value to predict SPH were 78.5% and 85.7% respectively with a PPV of 95.6% and an NPV of 50%. Tables 7 and 8 represent the predictive values of transient elastography for the prediction of severe portal hypertension (HVPG >12 mmHg).

Statistic	Value	95% CI
Sensitivity	78.57%	59.05% to 91.70%
Specificity	85.71%	42.13% to 99.64%
Positive Likelihood Ratio	5.5	0.89 to 34.11
Negative Likelihood Ratio	0.25	0.12 to 0.54
Disease prevalence	80.00%	63.06% to 91.56%
Positive Predictive Value	95.65%	78.01% to 99.27%
Negative Predictive Value	50.00%	31.62% to 68.38%
Accuracy	80.00%	63.06% to 91.56%

Table 8: Predictive values of TE cut-off for severe portal hypertension (HVPG >12 mmHg)

Median HVPG values in patients with TE values less than and greater than 16.5 kPa

The median HVPG in patients with TE values less than 16.5 kPa (the calculated cut-off to predict clinically significant portal hypertension) was 10.5 mmHg and in the sub-group with transient elastography value more than 16.5 kPa was 17 mmHg.

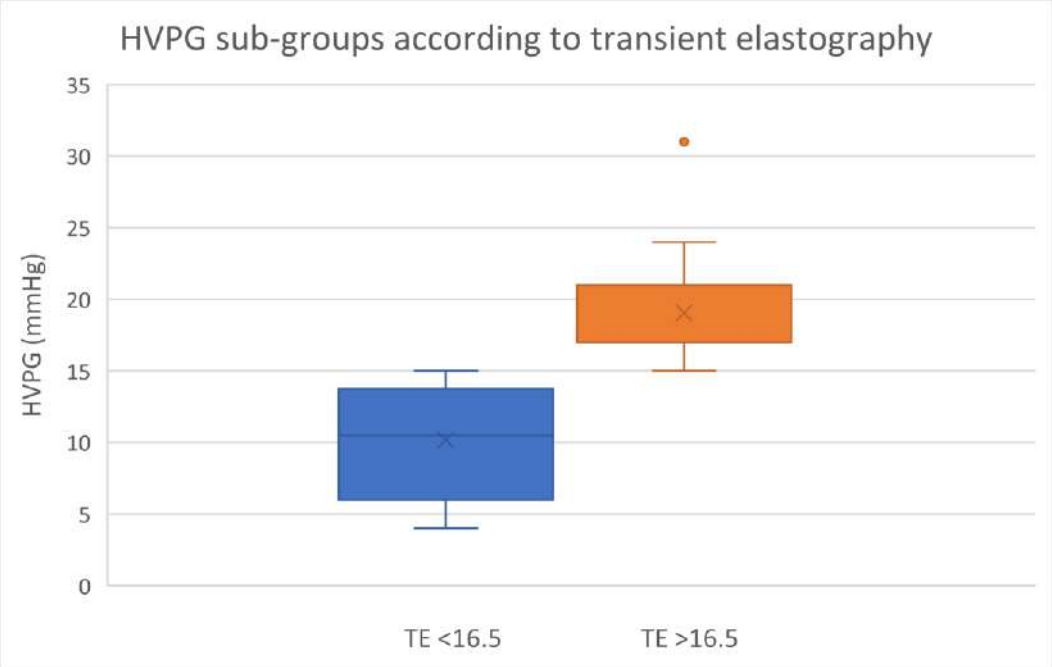

Fig 16.1: Median HVPG values in patients with TE values less than and greater than 16.5 kPa

Median HVPG values in patients with TE values less than and greater than 21.2 kPa

The median HVPG in patients with TE values less than 21.2 kPa (the cut-off to predict severe portal hypertension) was 14 mmHg and in the sub-group with transient elastography value more than 21.2 kPa was 19.5 mmHg.

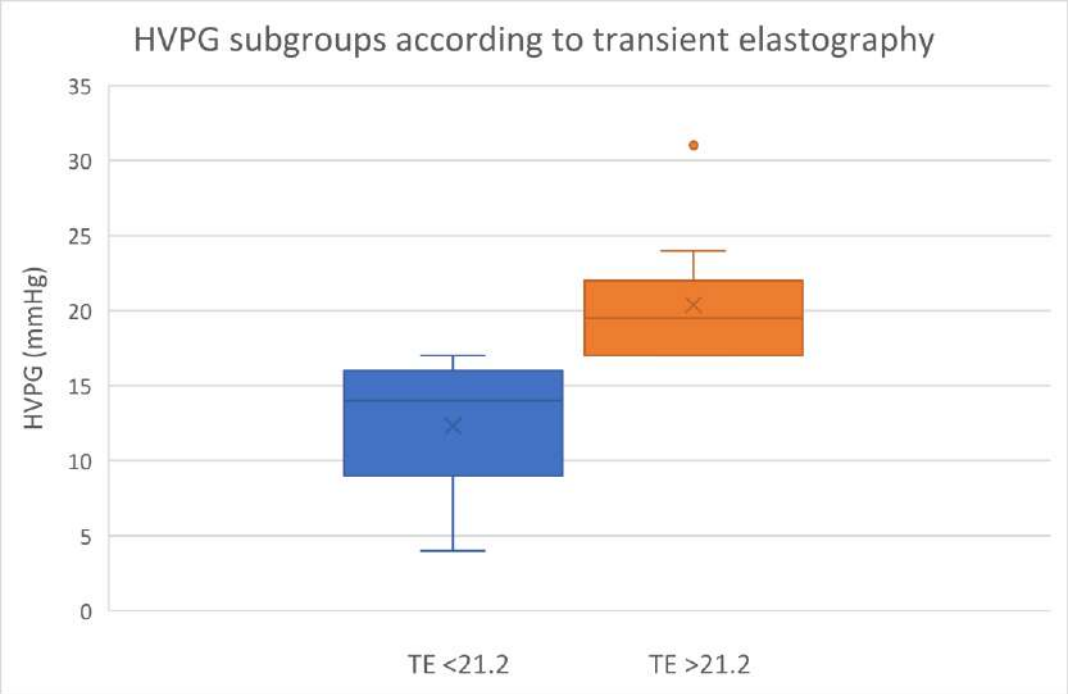

Fig 16.2: Median HVPG values in patients with TE values less than and greater than 21.2 kPa

Correlation of HVPG and TE values with increasing grades of varices

Median HVPG values in patients with different subgroups of esophageal varices

A positive correlation was noted between the HVPG values with increasing grades of esophageal varices, in the subset of patients who underwent upper GI endoscopy. The median HVPG values with their inter-quartile ranges in different subgroups of patients who underwent upper GI endoscopy are represented in Figure 17.1.

The median HVPG reading in the subgroup of patients who underwent UGI endoscopy but had no varices was 14 mmHg.

The median HVPG reading in the subgroup of patients who and had grade 1 varices was 16.5 mmHg.

The median HVPG reading in the subgroup of patients who demonstrated grade 2 varices was 18 mmHg.

The median HVPG reading in the subgroup of patients who had grade 3 varices was 21.5 mmHg.

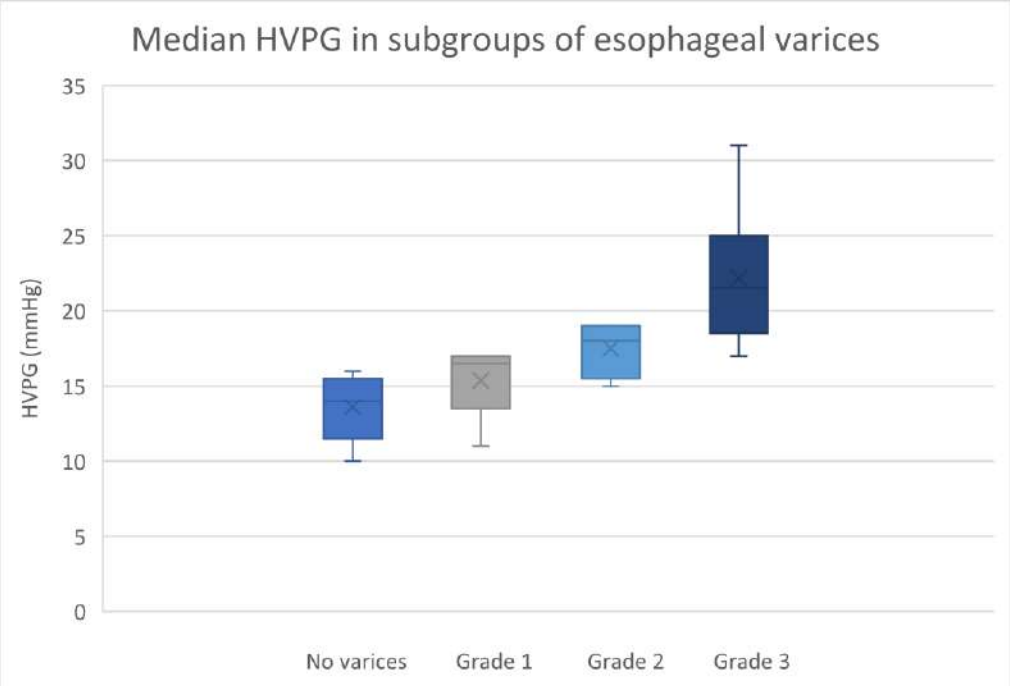

Fig 17.1: Median HVPG values in patients with different subgroups of esophageal varices

Median TE values in patients with different subgroups of esophageal varices.

Correspondingly, a positive correlation was noted between the TE values with increasing grades of esophageal varices, in the subset of patients who underwent upper GI endoscopy. The median TE readings with their inter-quartile ranges in different subgroups of patients who underwent upper GI endoscopy are represented in Figure 17.2.

The median TE value in the subgroup of patients who underwent UGI endoscopy but had no varices was 20.2 kPa.

The median TE value in the subgroup of patients who had grade 1 varices was 26.8 kPa.

The median TE value in the subgroup of patients who demonstrated grade 2 varices was 31.9 kPa.

The median TE value in the subgroup of patients who had grade 3 varices was 56.2 kPa.

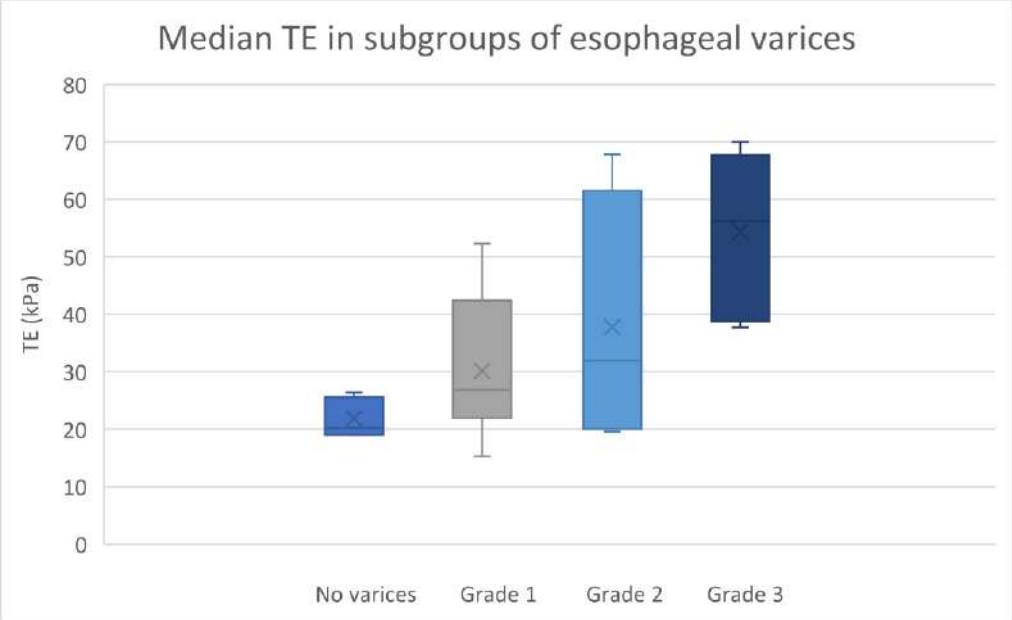

Fig 17.2: Median TE values in patients with different subgroups of esophageal varices.

DISCUSSION

Measuring the hepatic venous pressure gradient although an invasive procedure, is the ideal modality to quantify portal hypertension; thereby prognosticating morbidity and mortality in cirrhotic patients by predicting various complications caused due to rising portal pressures. The results of this study illustrate that in cirrhotic patients with portal hypertension, HVPG has a fair correlation with TE values.

A total of 35 cirrhotic patients with portal hypertension, who underwent HVPG measurements were included in our study. All of them underwent liver stiffness measurements by transient elastography. Thirty-eight patients were included in their study by Sanchez-Conde et al [51] in 2011, while Augustin et al [58] in 2014 studied 40 patients with cirrhosis and portal hypertension.

In this study, a male preponderance was noted, i.e. 65.7% of the patients were males and 34.2% were females. The male-to-female ratio was 1.9:1. Similarly, a male predominance was found in the studies conducted by Procopet et al [61] in 2015, Vizzuti et al [48] in 2007 and Berzigotti et al [55] in 2013, with 65%, 64% and 70% of their patients being males.

The median age of patients in our study was 51 years, with most of the patients falling into the age group of 51-60 years. In accordance, the median age of the cohort in the studies done by Reiberger et al [52], Zykus et al [59], Bureau et al [50] was 50, 52.3 and 55 years respectively.

Out of 35 patients, the commonest etiology for cirrhosis was NASH-related liver disease (45.7%), followed by alcoholic liver disease (22.8%). Kumar et al [64] had similar findings in their study with 45% of their patients suffering from NASH related/cryptogenic liver cirrhosis and 34% of the patients having cirrhosis due to alcoholic liver disease. However, most of the studies conducted in the West including those by Schwabl et al [63], Llop et al [53] and Berzigotti et al [55] had HCV/HBV-related cirrhosis as their predominant etiology. This could be related to the high prevalence of type 2 diabetes mellitus and non-alcoholic fatty

liver disease in India and South-East Asia as outlined by the data collected by Lim et al [3] and Unnikrishnan et al [5].

The median HVPG was 17 mmHg with a range of 4 to 31 mmHg. Kumar et al [64] and Lemoine et al [49] had a nearly similar median HVPG of 16 mmHg and 15 mmHg respectively, in their patient cohorts. However, most of the studies conducted in Europe had a lower value of median HVPG measurement. For instance, Kitson et al [62] and Reiberger et al [52] had median HVPG values of 12.1 and 12.6 mmHg respectively, while Hong et al [56] had a median HVPG value of 13.1 mmHg. This could be explained due to the fact that most of the patients in South-East Asia present in advanced stages of cirrhosis and portal hypertension.

The median liver stiffness value was 26.7 kPa with a range of 4.2 to 66.4 kPa. This was largely in accordance with the median TE values of Reiberger et al [52] who had a median TE value of 26.4 kPa and Berzogitti et al [55] who had a median TE value of 25.2 kPa in their cohorts. However, some of the studies had considerably lower median TE values, including that of Procopet et al [61] at 12 kPa, Bureau et al [50] at 17.1 kPa and Llop et al [53] at 17.3 kPa. Interestingly, Kumar et al [64] in their study encountered a noticeably higher median TE value at 36 kPa. This could have been due to the assumption that cirrhotic patients in South-East Asia and India present with higher degrees of liver fibrosis.

There was a fair correlation between HVPG and TE values, as observed by the scatterplot of our study (Spearman's rho 0.847, $p < 0.001$). There was a poorer correlation at higher TE values, as observed by the scatterplot of our study and that of the study conducted by Reiberger et al [52]. The slope of the trend line on the left side of the graph when the disease is less severe was steeper, indicating a better correlation compared with the right side when the trend line was flatter. Vizzutti et al [48] also found that the correlation was excellent for HVPG values less than 10 or 12 mmHg ($r = 0.81$ and $r = 0.91$, respectively); however, the linear regression analysis was not optimal for HVPG values ≥10 mmHg ($r = 0.59$) or >12mmHg ($r = 0.37$).

The TE values increased progressively as portal pressure increased from normal through subclinical, clinically significant, severe and very severe portal hypertension.

The median TE values for the HVPG subgroups with subclinical, clinically significant, severe and very severe portal hypertension were 13.9, 21.05, 26.5 and 52.8 kPa respectively. Following a similar expected pattern, the median TE values for the HVPG subgroups in the study conducted by Kumar et al [64] were 19, 26, 37 and 46 kPa respectively.

Although HVPG measurement is the gold standard for diagnosing clinically significant portal hypertension (CSPH), it is not in common use because it is invasive, not widely available, and expensive, thus hindering its broad use in diagnostic and therapeutic algorithms in patients with cirrhosis with CSPH. Our study found that a TE value of 16.4 kPa is a fairly accurate cut-off for predicting CSPH (i.e. HVPG ≥10 mmHg). It offers a high sensitivity of 96.6% with a specificity of 80%. It showed a PPV of 96% and an NPV of 80%. Furthermore, a TE cut-off value of 21.2 kPa was 78.5% sensitive and 85% specific for predicting severe portal hypertension (i.e. HVPG >12mmHg). It showed a high PPV of 95.6% with an NPV of 50%.

This was found to be in keeping with the study done by Zykus et al [59] who found the TE cut-offs of 17.4 kPa and 20.6 kPa as the best cut-offs to predict clinically significant and severe portal hypertension respectively. Similarly, Schwabl et al [63] found a nearly similar TE cut-off value of 16.1 kPa to best predict CSPH, offering sensitivity and specificity of 93.6% and 87% respectively. Salzl et al [38] again had a similar cut-off value at 16.8 kPa to predict CSPH with a sensitivity and specificity of 89.7% and 75% respectively. Vizzuti et al [48] and Reiberger et al [52] also had similar, albeit slightly higher cut-off values at 17.6 kPa and 18 kPa respectively, offering high sensitivities of 90% and 83%.

Llopet al [53] from Spain provided two cut-offs of TE instead of one to predict CSPH. They showed that a cut-off of 13.6 kPa was 91% sensitive to exclude CSPH, and a cut-off of 21 kPa was 91% specific to

include CSPH. They suggested that values in between these limits (which were found in 35% of their patients) were not useful.

They advocated that the use of at least two cut-offs reproduces the clinical thinking in which a diagnostic test commonly provides three outputs: the condition is included, excluded or the result is a “grey zone” where further tests are needed.

Berzigotti et al [55] also found out that a 13.6 kPa cut-off had high sensitivity: 91.0% (95% CI, 82.6%-95.6%), but low specificity 56.4% (95% CI, 41.0%-70.7%), while a 21.1 kPa cut-off had a 92.3% specificity (95% CI, 79.7%-97.3%), but low sensitivity: 65.4% (95% CI, 54.3%-75.0%) for the prediction of CSPH. The rest of the patients with values of TE between 13.6 and 21.1 kPa (29% of the included population) could be accurately classified and should be considered indeterminate.

However, we believe that multiple cut-offs may lead to confusion, and the single cut-off with a high PPV is best for guiding primary physicians in the community to make treatment decisions.

A few authors reported slightly differing cut-off values to that of ours. For instance, Sanchez et al [51] reported that a TE cut-off value of 14 kPa was able to predict CSPH with a positive predictive value of 83.8% and a negative predictive value of 71.4%. Meanwhile, Bureau et al [50] had higher cut-off values at 21 kPa with a PPV of 92.5% and NPV of 90.7%. Similarly, Hong et al [56] found that a cut-off of 21.9 kPa was able to predict CSPH with a PPV of 86.8%, although with an NPV of 66.7%.

This difference could be related to the fact that these studies have had different etiological profiles of cirrhotic patients. Most of the studies had more patients with a viral etiology, whereas our study had more patients with NASH-related/cryptogenic cirrhosis and alcoholic liver disease.

The second possible reason for the difference in the cut-off values was possibly the difference in the degree of liver fibrosis and portal hypertension. The median HVPG in our patients was 17 mmHg, as compared to median HVPG readings of 10 mmHg and 13.1 mmHg in

the studies conducted by Bureau et al [50] and Hong et al [56] respectively. The median liver stiffness (TE) value in our study was 26.7 kPa while the values obtained by Bureau et al [50] and Llop et al [53] were 17.1 kPa and 17.3 kPa respectively. This indicated that our patient cohort had a more severe degree of liver cirrhosis as compared to these studies, in congruence with the epidemiological profile of the Indian subcontinent. A third reason for the same could be that these studies had considerably larger patient cohorts.

Compared to the previous studies, our study reported a fair correlation of HVPG values with transient elastography measurements (Spearman's rho correlation coefficient 0.847, $p < 0.001$), although we suggest that similar studies in the future should be undertaken with a larger patient cohort for better statistical significance.

SUMMARY AND CONCLUSION

1. The present study was conducted at the department of Radiodiagnosis, Dayanand Medical College and Hospital, Ludhiana.
2. 35 cirrhotic patients with portal hypertension who underwent HVPG and TE measurements over a period of 1 year were included in the study.
3. The age range of the patients was 18 to 75 years (23 males, 12 females); with most patients belonging to the age group of 51-60 years.
4. The commonest etiology for cirrhosis in our study was NASH-related liver disease (45.7%) followed by alcoholic liver disease (22.8%).
5. The median HVPG measurement was 17 mmHg with a range of 4 to 31 mmHg. The median transient elastography value was 26.7 kPa with a range of 4.2 to 66.4 kPa.
6. A fair correlation was noted between liver stiffness and HVPG levels. The correlation was better at lower HVPG and TE values.
7. There was a progressive rise in median TE values with increasing stages of portal hypertension.
8. A TE cut-off of 16.5 kPa predicted CSPH with a sensitivity and specificity of 96.6% and 80.0% respectively, with a positive predictive value of 96% and a negative predictive value of 80%.
9. There was a progressive increase in the grades of esophageal varices with rising HVPG and TE values.
10. TE may be used as a non-invasive modality to predict the development of clinically significant portal hypertension.

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Sr. No.	Name	MRD no.	Age	Gender	Etiology of cirrhosis	OT/PT/ALP	T. bil/D.bil	S. protein/ S. albumin	VM	Others	Ascites	UGI bleed	HE	CPS	HVPG (mmHg)	TE (kPa)	UGIE
1	SK	299123	51	female	?NASH related	26/33/68	0.34/0.14	8.1/4.3	NR	-	no	no	no	5 (A)	4	4.2	NA
2	PS	396194	43	male	HBV related	58/41/98	0.48/0.11	7/3.5	HBsAg +	-	no	no	no	5 (A)	5	10.5	NA
3	HK	51663	56	female	?NASH related	19/16/149	0.35/0/14	6.7/4.8	NR	-	no	no	no	5 (A)	5	12.1	NA
4	KB	768197	56	male	?NASH related	60/38/104	0.58/0.21	6.9/3.7	NR	-	no	no	no	5 (A)	9	15.7	NA
5	JS	492884	70	male	alcoholic liver disease	157/136/163	7.3/4.4	5.2/2.4	NR	-	no	no	no	7 (B)	9	17.2	NA
6	UK	328168	60	female	?NASH related	50/28/95	0.52/0.25	8/4.2	NR	-	no	no	no	5 (A)	10	19.1	PHG; no varices
7	KM	194809	55	male	?NASH related	29/29/104	1.6/0.9	7.6/4.4	NR	-	no	no	no	5 (A)	11	23	grade 1 varices
8	RK	367570	28	female	?NASH related	71/39/111	1.4/1.1	6.3/3.1	NR	-	no	no	no	6 (A)	13	21.6	early varices (gr 1)
9	VS	585645	52	male	NASH related	58/46/360	2.5/1.25	4.6/2.0	NR	-	yes (mild)	no	no	8 (B)	13	20.2	no varices
10	PS	742200	67	female	?autoimmune ?NASH	44/17/106	1.5/0.4	6.5/3.0	NR	-	no	no	no	6 (A)	14	19	no varices
11	MHD. A	776694	67	male	?drug induced	38/10/300	2.09/2.08	6.2/2.3	NR	-	no	no	no	8 (B)	14	21.3	NA
12	RK	673248	55	male	alcoholic liver disease	57/35/154	0.9/0.3	7.2/3.8	NR	-	no	no	no	5 (A)	15	15.3	grade 1 varices
13	DK	199670	53	female	infective (hepatitis C)	41/49/136	0.58/0.21	6.1/3.6	HCV +	-	no	no	no	5 (A)	15	21.2	grade 2 varices
14	HB	491194	44	male	?NASH related	51/24/84	1.02/0.39	6.7/2.6	NR	-	no	no	no	7 (B)	15	24.7	PHG; no varices
15	V	635194	42	female	?NASH related	99/178/487	1.44/0.55	6.0/3.0	NR	-	no	no	no	5 (A)	16	26.4	mild PHG
16	VSB	574720	24	male	?drug induced liver injury	114/120/280	1.5/0.6	7.4/4.2	NR	-	no	no	no	5 (A)	16	28.1	esophageal varices +
17	VP	706413	54	male	Infective (hpatitis B)	75/44	1.6/1	7/5.7	HBsAg +	-	yes (mild)	no	no	6 (A)	16	30.9	NA
18	SS	783780	18	male	?drug induced liver injury	74/30/275	1.8/1.5	6.3/3.7	NR	-	no	no	no	5 (A)	17	19.2	NA
19	JSS	854976	65	male	? Autoimmune	97/90/107	2.3/1.2	8.0/3.6	NR	ANA 4+	no	no	no	6 (A)	17	19.6	grade 2 varices
20	VA	620090	58	male	alcoholic liver disease	74/27/500	11.8/11.2	5.9/1.9	NR	-	no	no	no	9 (B)	17	26.7	fundal varices +
21	NM	263018	18	male	?autoimmune	57/57/300	2.1/0.9	8.2/3.0	NR	-	no	no	no	7 (B)	17	27	early varices (gr 1)
22	HS	678717	51	male	alcoholic liver disease	31/20/43	0.6/0.2	4.4/2.1	NR	-	no	yes	no	7 (B)	17	39.1	grade 3 varices
23	AG	811260	62	male	?NASH related	85/37/122	2.5/2.1	7.0/2.57	NR	-	no	no	no	9 (B)	17	47.2	grade 1 varices x3
24	S	668688	28	female	?NASH related	115/77/193	2.3/0.8	6.9/3.1	NR	-	no	no	no	7 (B)	17	52.3	grade 1 varices x2
25	YM	685758	65	male	?drug induced liver injury	76/42/109	1.4/0.4	5.2/2.5	NR	-	no	no	no	7 (B)	19	42.6	grade 2 varices x2
26	AS	138019	48	male	?NASH related	32/26/82	0.6/0.2	6.7/2.9	NR	-	no	yes	no	6 (A)	19	66.9	grade 3 varices x3
27	SC	534634	51	male	alcoholic liver disease	36/39/191	1.4/0.2	8.2/4.3	NR	-	no	no	no	5 (A)	19	67.8	grade 1 varices x2
28	JK	901544	20	female	?autoimmune	179/71/129	1.4/0.7	9.1/2.2	NR	ANA 2+, ASMA 3+	no	no	no	7 (B)	20	66.9	NA
29	SK	829158	18	female	?autoimmune	95/103/227	2.1/1.6	6.4/2.7	NR	ANA 2+, ASMA +	no	no	no	8 (B)	21	27.8	no varices
30	TR	650396	75	male	NASH related	48/39/77	2.5/1.0	6.1/3.3	NR	-	no	yes	no	7 (B)	21	70	grade 3 varices x2
31	KK	526444	50	female	?NASH related	129/49/445	14.0/12.0	7/2.7	NR	-	no	no	no	9 (B)	22	54.2	NA
32	BS	650390	37	male	alcoholic liver disease	78/42/74	1.8/0.8	6.3/3.6	NR	-	no	yes	no	7 (A)	22	37.7	grade 3 varices
33	RS	706512	68	male	alcoholic liver disease	90/51/253	1.2/0.7	6.0/2.7	NR	-	no	yes	no	8 (B)	23	46	grade 3 varices x3
34	KK	722420	62	female	?NASH related	74/70/73	2.4/1.9	6.3/2.8	NR	-	no	no	no	7 (B)	24	51.4	NA
35	DL	749245	51	male	alcoholic liver disease	67/21/90	13.8/8	7.3/2.8	NR	-	no	yes	no	10 (C)	31	66.4	grade 3 varices x3

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Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 29.05.2019 has approved the plan of thesis of **Kanav Grover**, a student of your college for **MD Radio-Diagnosis** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis

Correlation of hepatic venous pressure gradient with transient elastography in patients with cirrhotic portal hypertension

Supervisor
Dr. Siddharth Prakash
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Co-Supervisor
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The student has to submit the four copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

SP Singh
Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

1. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*
2. *The student may submit the thesis as per the schedule already conveyed i.e for May/June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination.*

CORRELATION OF HEPATIC VENOUS PRESSURE GRADIENT WITH TRANSIENT ELASTOGRAPHY IN PATIENTS WITH CIRRHOTIC PORTAL HYPERTENSION

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

Doctor of Medicine
in

RADIODIAGNOSIS

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES
FARIDKOT

AUGUST, 2018

DR. KANAV GROVER

DEPARTMENT OF RADIODIAGNOSIS
DAYANAND MEDICAL COLLEGE AND HOSPITAL
LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	CORRELATION OF HEPATIC VENOUS PRESSURE GRADIENT WITH TRANSIENT ELASTOGRAPHY IN PATIENTS WITH CIRRHOTIC PORTAL HYPERTENSION
For the degree of	MD RADIODIAGNOSIS
Name of the candidate	Dr Kanav Grover
Supervisor	Dr Siddharth Prakash Associate Professor Department of Radiodiagnosis
Co-supervisor(s)	Dr Varun Mehta Associate Professor Department of Gastroenterology Dr Archana Ahluwalia Professor Department of Radiodiagnosis
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction:
The end result of ongoing insult to the liver due to any cause is hepatic fibrosis, cirrhosis and the development of portal hypertension. The progression of portal hypertension can predict various complications of cirrhosis. Hepatic venous pressure gradient (HVPG) is the ideal method for the measurement of portal hypertension and the prediction of complications, however, HVPG is an invasive procedure that requires expertise. Transient elastography (TE) is a non-invasive, ultrasound-based technology that measures the degree of liver fibrosis and hence cirrhosis, suggesting that it could be a good non-invasive tool for evaluation of portal hypertension.

Aims of Study:
To identify a possible correlation between HVPG and transient elastography in cirrhotic and to investigate whether TE can serve as a non-invasive modality to identify patients who have clinically significant portal hypertension.

Material & Methods:
The study will be conducted at Dayanand Medical College and Hospital, Ludhiana; on consecutive patients who undergo HVPG and TE during a specific period. Correlation between HVPG and TE will be analysed using ROC curves to determine the utility of TE in predicting various stages of portal hypertension.

Clinical Significance:
Clinically significant portal hypertension (CSPH), which is defined as HVPG ≥ 10 mmHg, causes major complications of cirrhosis. HVPG is invasive, so a non-invasive tool to diagnose CSPH is needed.

Keywords: Liver cirrhosis, HVPG, Liver stiffness, CSPH, transient elastography

(Signature)	(Signature)	(Signature)	(Signature)	(Signature)
Candidate	Co-supervisor	Co-supervisor	Supervisor	Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"CORRELATION OF HEPATIC VENOUS PRESSURE GRADIENT WITH TRANSIENT ELASTOGRAPHY IN PATIENTS WITH CIRRHOTIC PORTAL HYPERTENSION"** exist in the Department of Radiodiagnosis, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate himself under our supervision and guidance.

Supervisor

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Co-Supervisor(s)

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Place : 21/12/18 (Ludhiana)
Date : 21/12/18

APPROVAL PROFORMA
BY
RESEARCH & ETHICAL COMMITTEE
DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

Name of candidate	DR. Kanav Grover
Department	Radiodiagnosis
Topic of Thesis	CORRELATION OF HEPATIC VENOUS PRESSURE GRADIENT WITH TRANSIENT ELASTOGRAPHY IN PATIENTS WITH CIRRHOTIC PORTAL HYPERTENSION
Likely date of appearing in PG examination	May 2021
Date of enrollment	10th May, 2018
Name of Head of Department	Dr. Kavita Saggar
1) Supervisor **2) Co-Supervisor(s)**	Dr. Siddharth Prakash Dr. Varun Mehta Dr. Archana Ahluwalia
Signature of Members of Research Committee with Stamp	**Signature of Members of Ethics Committee with Stamp**
1. HOD Pharmacology	1. HOD Physiology
2. HOD Surgery	2. HOD Pathology
3. HOD Pathology	3. HOD Pharmacology
4. HOD Medicine	4. HOD SPM
5. Dean Academics	5. HOD Medicine
6. Vice Principal	6. HOD Surgery
	7. HOD Obst. & Gynae
	8. Legal Expert
	9. Secretary, IEC
	10. Dean Academics
	11. Vice Principal
	12. Principal

Approved: Yes / No

Chairperson
Research Committee

Chairperson
Research Committee

Approved: Yes / ~~No~~

Chairperson
Ethics Committee

Chairperson
Ethics Committee

BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT

PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

1	NAME OF THE CANDIDATE AND ADDRESS	Dr. Kanav Grover #3, Pink Avenue, Majitha Road, Amritsar Punjab-143001
2	NAME OF THE INSTITUTE	Dayanand Medical College and Hospital, Ludhiana
3	COURSE OF STUDY AND SUBJECT	MD Radiodiagnosis
4	DATE OF ADMISSION OF COURSE	10-05-2018
5	TITLE OF THE TOPIC	CORRELATION OF HEPATIC VENOUS PRESSURE GRADIENT WITH TRANSIENT ELASTOGRAPHY IN PATIENTS WITH CIRRHOTIC PORTAL HYPERTENSION

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

The end result of ongoing injury to the liver due to any cause is hepatic parenchymal fibrosis and cirrhosis, and eventually the development of portal hypertension. The measurement of portal hypertension is important, as a progressive increase in portal pressure is believed to predict various complications of cirrhosis.[1]

Although cirrhosis mortality has been steadily decreasing globally and especially in the West, it has been steadily increasing in India since 1980. Alcohol consumption (the commonest cause of cirrhosis in India) and the prevalence of diabetes [a major risk factor for non-alcoholic fatty liver disease (NAFLD)] has been steadily increasing in South Asia. With 188,575 liver cirrhosis deaths in 2010, India ranks number one in the world in liver cirrhosis deaths, accounting for almost one-fifth (18%) of global liver cirrhosis deaths.[2] With such a huge population of liver cirrhosis patients in India whose aetiology differs from the West, an easy and non-invasive modality for estimation of portal hypertension is urgently needed for treating these patients. Our study attempts to address this need for Indian and South Asian populations.

Hepatic venous pressure gradient (HVPG) is the ideal method for the measurement of portal hypertension and the prediction of complications.[3] Porto-systemic collaterals develop at HVPG greater than 10 mmHg, and variceal bleeding could occur from varices when the pressure increases to greater than 12 mmHg. An HVPG greater than 10 mmHg is used as the cut-off for "**clinically significant portal hypertension**" (CSPH).[4]

However, HVPG is an invasive procedure that requires training and expertise.

Many non-invasive tests have been reported to predict the presence of CSPH in patients with cirrhosis with variable accuracy. The ideal non-invasive diagnostic test for portal hypertension should be simple, inexpensive, widely accessible and reliable in measurement and interpretation.

Transient elastography (TE) is a non-invasive, ultrasound-based technology that allows the measurement of liver stiffness and has good sensitivity and specificity for diagnosing liver fibrosis and cirrhosis.[5]

Some European studies have reported a fairly good correlation between HVPG, liver stiffness and portal hypertension.

Thus, there is an urgent need for a South Asian study as the etiological and clinical picture of chronic liver disease is different from other regions of the world and the result of Western studies may not apply to the above population.

6.2 REVIEW OF LITERATURE

A few previous studies have correlated hepatic venous pressure gradient (HVPG) with transient elastography. The earliest of these studies was by Carrion et al from Spain (2006), who correlated transient elastography and hepatic venous pressure gradient in 124 patients. They identified a significantly high correlation of transient elastography with HVPG [Correlation coefficient(*r*) = 0.840].[6]

Similar studies have since been performed in by Vizzuti et al (Italy - 2007), Lemoine et al (France - 2008) and Bureau et al (France - 2008) who demonstrated significant correlations between HPVG and transient elastography with (r) values of 0.810, 0.530 and 0.858 respectively.[7,8] Vizzutti et al also found that the correlation was excellent for HVPG values less than 10 or 12 mmHg (r = 0.81 and r = 0.91, respectively); however, the linear regression analysis was not optimal for HVPG values ≥ 10 mmHg (r = 0.59) or ≥ 12 mmHg (r = 0.37). In advanced portal hypertension, it is not only the liver fibrosis but also the extrahepatic factors, such as the increase in blood flow due to hyperdynamic circulation, that contribute to portal hypertension.

The largest of these studies has been done by Reiberger et al (Austria – 2012), who retrospectively correlated transient elastography and HVPG in 502 patients and found a very high correlation between them (r – 0.799, P <0.0001).[9]

These studies have calculated the cut-off transient elastography values for diagnosing clinically significant portal hypertension (CSPH). These studies were performed in patients with different disease severities and different

proportions of viral cirrhosis, and their cut-off values ranged from 13.6 kPa to 65.3 kPa. The weighted mean of cut-off from all these studies was 21.9 kPa.

Notably, Llop et al from (Spain – 2012) provided two cut-offs of TE instead of one to predict CSPH. They showed that a cut-off of 13.6 kPa was sufficiently sensitive to exclude CSPH, and a cut-off of 21 kPa was sufficiently specific to include CSPH. They suggested that values in between these limits (which were found in 35% of their patients) were not useful. Some authors believe that the use of a single TE cut-off, although simple, limits the value of TE to predict CSPH. The use of at least two cut-offs reproduces the clinical thinking in which a diagnostic test commonly provides three outputs: the condition is included, excluded or "further tests are needed.[10]

A recent meta-analysis by Kim et al (Korea – 2016) comparing HVPG and TE for diagnosing portal hypertension demonstrated that TE showed high accuracy for detecting the severity of portal hypertension. [95% confidence interval (CI), $P < 0.0001$)].[11]

Another recent meta-analysis by Shi et al which included 5 studies of the diagnostic accuracy of TE for significant portal hypertension, also indicated that TE had a high accuracy for the detection of significant portal hypertension. The hierarchical summary receiver-operating characteristic (HSROC) for the diagnosis of significant portal hypertension by TE was 0.93 (95%CI: 0.90-0.95).

Therefore, TE showed promise as a reliable and non-invasive procedure for the evaluation of portal hypertension that should be integrated into clinical practice.[12]

The Fagan plot analysis showed that TE could be used to diagnose significant portal hypertension (when pre-test probability = 50%), with 81% probability of correctly diagnosing significant portal hypertension following the "positive" measurement. Furthermore, a "negative" measurement was also informative, as significant portal hypertension was present in only 11% of patients. However, when the pre-test probability of significant portal hypertension was as low as 25%, the probability of correctly identifying significant portal hypertension decreased markedly. These finding suggests that an accurate selection of patients is necessary to exploit the performance of TE at its best.[12]

Other newer and promising non-invasive modalities are being developed for diagnosing portal hypertension, such as two-dimensional shear wave elastography (2D-SWE)[13-17] and spleen elastography.[18,19] These tests have their own advantages and disadvantages. However, to date, very few studies have been performed on them for correlation with HVPG, so their routine use cannot be recommended outside of clinical trials.

6.3 AIMS AND OBJECTIVES OF THE STUDY

- To identify a possible correlation between HVPG and transient elastography in cirrhotic patients;
- To investigate whether TE can serve as a non-invasive diagnostic test to identify patients who have clinically significant portal hypertension

7. MATERIALS AND METHODS

7.1 Source of Data

The study will be conducted at Dayanand Medical College and Hospital, Ludhiana; on patients who undergo HVPG and TE during a specific period. Each included patient will undergo a detailed evaluation in terms of demographic parameters, aetiology of cirrhosis, assessment of severity of liver disease, and assessment of severity of portal hypertension. A standard methodology will be followed for the measurement of liver stiffness by TE and measurement of HVPG.

7.2 METHOD OF COLLECTION OF DATA

The study will be retrospective on prospectively enrolled patients during this period.

INCLUSION CRITERIA

Consecutive patients with cirrhosis greater than 18 years of age who undergo HVPG and TE will be included in the study.

EXCLUSION CRITERIA-

The following patients will be excluded from the study:

(1) Patients with non-cirrhotic cause of portal hypertension;

(2) Patients with acute-on-chronic liver failure;

(3) Patients with an invalid reading of TE or whose HVPG was not possible due to technical reasons.

(4) Patients with a concomitant extra-hepatic malignancy

DURATION OF STUDY

One year

OUTCOME

To identify a possible correlation between HVPG and transient elastography in patients with liver cirrhosis and to investigate whether TE can serve as a non-invasive diagnostic modality to identify patients who have clinically significant portal hypertension.

TOOLS

- **HVPG** will be measured by introducing a catheter via the transfemoral or transjugular approach into a major hepatic vein. The catheter will be advanced until it is wedged into the hepatic vein.
- **Liver stiffness** measurement will be performed using TE (*fibroscan*). Measurements will be performed on the right lobe of the liver through intercostal spaces with the patient lying in a supine position with the right arm in maximal abduction. The results will be expressed in kilopascals (kPa). All liver stiffness measurements will be performed by a single operator
- **Socio demographic proforma** will include the demographic parameters of the patient, aetiology of cirrhosis, assessment of severity of liver disease, and assessment of severity of portal hypertension. A standard methodology will be followed for the measurement of liver stiffness by TE and measurement of HVPG.

STATISTICAL ANALYSIS

Data will be described in terms of range; mean ±standard deviation (±SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. Correlation between HVPG and TE will be analysed using the Spearman's correlation test. Receiver operating

characteristic (ROC) curves will be prepared for determining the utility of TE in predicting various stages of portal hypertension. All statistical calculations will be done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

1) HEPATIC VENOUS PRESSURE GRADIENT

It is the difference between the wedged hepatic venous pressure (WHVP) and the free hepatic venous pressures. It represents the gradient between pressures in the portal vein and the intra-abdominal portion of inferior vena cava. When blood flow in a hepatic vein is stopped by a wedged catheter (WHVP), the proximal static column of blood transmits the pressure from the preceding communicating hepatic sinusoids to the catheter. Thus, WHVP reflects hepatic sinusoidal pressure and not the portal pressure itself, in the normal liver.

In liver cirrhosis, the static column created by balloon inflation cannot be decompressed at the sinusoidal level due to disruption of the normal intersinusoidal communications; therefore, WHVP gives an accurate estimation of portal pressure in cirrhosis

The normal HVPG value is between 1 to 5 mmHg. Pressure higher than this defines the presence of portal hypertension. HVPG >/= 10 mmHg (termed clinically significant portal hypertension) is predictive of the development of complications of cirrhosis; HVPG above 12 mmHg being the threshold pressure for variceal rupture.

2) TRANSIENT ELASTOGRAPHY

The basic principle of TE is that the propagation velocity of a wave through a homogenous tissue is proportional to its elasticity, which is correlated with the amount of fibrosis in the liver.

TE consists of an ultrasound transducer mounted on the axis of the vibrator, which produces vibration of a mild amplitude and low frequency (50 Hz), consequently inducing an elastic shear wave that propagates through the liver. Pulse-echo ultrasound follows the propagation of the shear wave and measures its velocity, which is related to liver tissue stiffness. It is seen that the velocity of elastic waves is faster in fibrotic liver than normal livers.

The reading is measured in KiloPascals (kPa).

7.4 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Attached herewith

8. LIST OF REFERENCES

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PROFORMA

S.No.

Name of patient: MRD no:

Age/Sex: Consultant:

Address: Date:

Phone no:

Indication:

Clinical data:

Etiology of CLD/cirrhosis:

Viral markers : HBsAg

HCV

HIV

Complications : Ascites

UGI bleed

Hepatic encephalopathy

PRE PROCEDURAL WORK-UP

Hb -

TLC -

Platelets -

PT/INR -

LFTs : T bilirubin -

D bilirubin -

Signature of Candidate **Signature of Supervisor**

S. Protein -

S. Albumin -

SGOT/SGPT/ALP -

RFTs : S. Urea -

S. creatinine -

Child-Pugh Score-

UGI ENDOSCOPY

TRANSIENT ELASTOGRAPHY (Fibroscan)

ULTRASOUND

HEPATIC VENOUS PRESSURE GRADIENT

Free HPV:

Wedge HPV:

IVC pressure:

RA pressure:

HVPG (Wedge HVP – Free HVP)

Signature of Candidate **Signature of Supervisor**

INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o.....

.....am willing to participate in the study **"CORRELATION OF HEPATIC VENOUS PRESSURE GRADIENT WITH TRANSIENT ELASTOGRAPHY IN PATIENTS WITH CIRRHOTIC PORTAL HYPERTENSION"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

.....
Signature of the Witness

Name:

.....
Signature of the patient

Signature of Candidate

Signature of Supervisor

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य **"CORRELATION OF HEPATIC VENOUS PRESSURE GRADIENT WITH TRANSIENT ELASTOGRAPHY IN PATIENTS WITH CIRRHOTIC PORTAL HYPERTENSION"** में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____

गवाह के हस्ताक्षर रोगी के हस्ताक्षर/अंगूठे का निशान

नाम: नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

"CORRELATION OF HEPATIC VENOUS PRESSURE GRADIENT WITH TRANSIENT ELASTOGRAPHY IN PATIENTS WITH CIRRHOTIC PORTAL HYPERTENSION" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

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ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

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ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

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ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ